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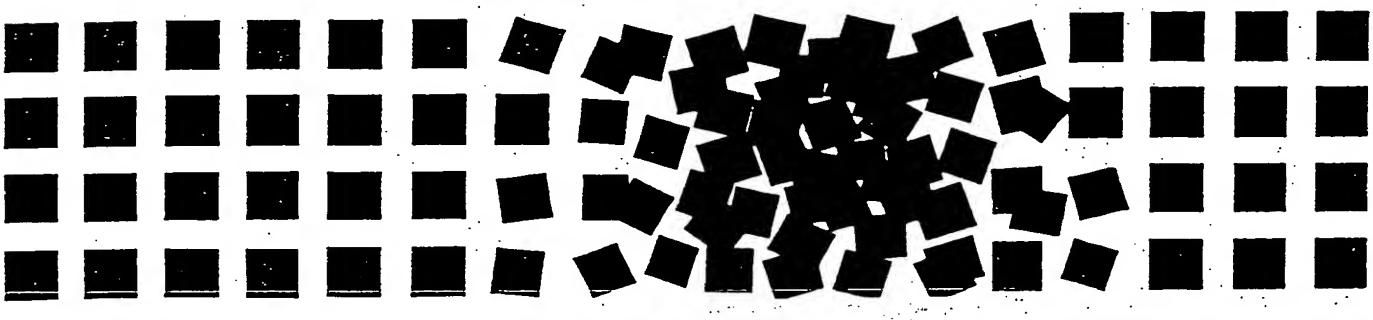

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SECTION 5

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Cancer of the Liver and Biliary Tree

Primary hepatobiliary malignancies are the most common of solid-organ cancers, and include hepatocellular carcinomas (HCCs), cholangiocarcinomas, and gallbladder cancers. As a group, these tumors represent both major diagnostic and therapeutic challenges. Though surgery can be potentially curative for these tumors, until recently, most cases of hepatobiliary cancers were discovered at a stage far too advanced for complete excision. These tumors also are highly resistant to chemotherapy, limiting options for palliative treatment. However, the last two decades have seen great advances in the diagnosis of and therapy for these tumors. Advances in imaging have allowed for earlier detection and more accurate staging of disease. The safety of surgical therapy has improved and, as a consequence of increased understanding of the biology of these diseases, favorable short- and long-term results are increasingly achieved by extensive but rational resection. Palliative measures such as radiotherapy and ablative therapy have extended the limits of tumor eradication and treatment. In this chapter, a discussion of the current therapy for these hepatobiliary tumors will be presented, emphasizing the recent major advances as well as the most important areas of ongoing and future studies.

HEPATOCELLULAR CARCINOMA

HCC is the most common solid-organ tumor worldwide, being responsible for more than 1 million deaths annually. The difficulties in treating HCC and the high mortality associated with it are attributable to a number of factors. First, this cancer usually is associated with cirrhosis, which is not only a cause of morbidity but also limits treatment options for the cancer. Second, HCC is usually asymptomatic at early stages and has a great propensity for intravascular or intrabiliary extension, even when the primary tumor is small. As a result, the carcinoma is usually at an advanced stage when discovered. This tumor is, therefore, usually beyond curative therapy at presentation and, indeed, often beyond any useful therapy.

EPIDEMIOLOGY AND ETIOLOGY

At least 1 million new cases of HCC occur yearly.[1] The incidence of HCC increases with age and is four to eight times more common in men than in women.[2] This cancer is clearly associated with chronic liver injury and, therefore, geographic distribution of HCC closely mirrors that of viral hepatitis (Table 33.5-1). Countries with a high incidence of hepatitis B virus (HBV) infection—namely Taiwan, Korea, Thailand, Hong Kong, Singapore, Malaysia, China, and countries of tropical Africa—have the highest incidence of HCC.[3–5] Areas in which hepatitis C virus (HCV) infections are endemic, such as Japan and Italy, also experience an increased rate of HCC.[3,6–10] In these areas, incidence varies from a high of 150 per 100,000 in Taiwan[3] to 28 per 100,000 in Singapore.[4] Comparatively, in low-incidence areas such as Australia, North America, and Europe, HCC occurs in only 1 to 3 per 100,000 population. In high-incidence areas, HCC also occurs in younger individuals as compared to its occurrence in low incidence areas. In Mozambique, one of the areas of highest incidence of HCC, 50% of patients with the tumor are younger than 30 years. In fact, the incidence of HCC among men aged 25 to 34 years is more than 500-fold that of the same age group in Western countries.[11]

TABLE 33.5-1. Conditions Predisposing to or Associated with Development of Hepatocellular Carcinoma

INFECTIONS
Hepatitis B virus
Hepatitis C virus
CIRRHOSIS
Alcohol
Autoimmune hepatitis
Primary biliary cirrhosis
Cryptogenic cirrhosis
ENVIRONMENT
Androgenic steroid
Aflatoxins
Tobacco
N-nitrosylated compounds
Pyrrolizidine alkaloids
Thorotrast
METABOLIC DISEASES
Hemochromatosis
α_1-Antitrypsin deficiency
Wilson's disease
Porphyria cutanea tarda
Types 1 and 3 glycogen storage disease
Galactosemia
Citrullinemia
Hereditary tyrosinemia
Familial cholestatic cirrhosis

This etiologic association between HBV infection and HCC is well established. In a landmark study examining HBV infection and HCC, Beasley et al.[12] followed 22,707 male subjects in Taiwan, 15.2% of whom were HBV chronic carriers, as exhibited by detection of hepatitis B surface antigen (HB_sAg) in the serum. Of the 116 cases of HCC that occurred during a mean follow-up period of 7 years, 113 occurred in patients positive for HB_sAg. This study demonstrated that HCC was related not simply to a history of HBV infection but to the chronic carrier states and that the relative risk of developing HCC was 200-fold greater in individuals with evidence of HBV infection than in noninfected individuals.[12]

Epidemiologic evidence has also clearly linked HCV infection with HCC. Antibodies to HCV have been found in as many as 76% of patients with HCC in Japan, Italy, and Spain[13] and in

in the United States.[14] In contrast to HBV-associated HCC, however, HCC rarely occurs in HCV carriers before the development of cirrhosis. In addition, the incidence of HCC in cirrhotic carriers of HCV is estimated to be as high as 5% per year, compared to 0.5% per year for HBV carriers.[15]

Chemical carcinogens also have been linked to primary liver cancers. Chemicals such as nitrites, hydrocarbons, solvents, organochlorine pesticides, primary metals, and polychlorinated biphenyls have been implicated in the development of HCC.[16] Colloidal thorium dioxide (Thorotrast), which emits high level α, β, and γ radiation and was used as an angiographic agent in the 1930s, has been linked to angiosarcoma, cholangiocarcinoma, and HCC.[1]

Of all the chemicals linked to development of HCC, the most important is ethanol. Alcohol abuse has been linked to the development of not only HCC but also carcinomas in the larynx, mouth, and esophagus. Ethanol is thought to produce HCC through development of hepatic cirrhosis or as a cocarcinogen with other agents such as HBV, HCV, hepatotoxins, and tobacco,[17–22] rather than through direct effect on the hepatocytes.

Aflatoxins produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus* have also been linked to HCC. These are fungi that grow on grains, peanuts, and other food products and are the most common cause of food spoilage in the tropics. These fungi produce aflatoxins designated as B_1, B_2, G_1, and G_2. Aflatoxin B_1 is the most hepatotoxic, and chronic exposure to these mycotoxins leads to development of HCC.[23]

Some congenital conditions also lead to development of HCC. Genetic diseases such as hemochromatosis, Wilson's disease, hereditary tyrosinemia, type 1 glycogen storage disease, hepatic porphyria of both intermittent and cutanea tarda types, familial polyposis coli, ataxia telangiectasia, familial cholestatic cirrhosis, biliary atresia, congenital hepatic fibrosis, neurofibromatosis, situs inversus, fetal alcohol syndrome, α-antitrypsin deficiency, and the Budd-Chiari syndrome[11] have all been linked to a higher incidence of HCC. Ultimately, though, the unifying etiology of HCC may be chronic injury and inflammation.

PATHOLOGIC FEATURES

HCC has been graded as well differentiated, moderately well differentiated, and poorly differentiated. The well-differentiated variety may be difficult to distinguish from a regenerating nodule on fine-needle biopsy. No firm correlation of grade to prognosis has been established. HCC can be classified generally into three different growth patterns, and these growth patterns have a much greater influence than does histologic grade on resectability and, therefore, greater influence on long-term outcome. The hanging type of tumor is attached to the normal liver by a small vascular stalk, even if the tumor is large. This type is easily excised with little loss in functional parenchyma. The pushing type generally is well demarcated and often encapsulated by a fibrous capsule. This type of tumor displaces normal vasculature rather than infiltrates and invades the major vessels. It is often resectable, even when tumor bulk is substantial. Finally, the infiltrative variety has a very indistinct tumor-liver interface and tends to exhibit a much greater degree of vascular infiltration and invasion, even when the tumor is small. Excising the infiltrative variety often is complicated by positive margins. The practical nature of this gross pathologic classification is reinforced by the distinctive radiologic appearance of these three different growth patterns on imaging.

TABLE 33.5-2. Comparison of Standard Hepatocellular Carcinoma with the Fibrolamellar Variant

Characteristic	*HCC*	*Fibrolamellar HCC*
Male-female ratio	4:1–8:1	1:1
Median age	55	25
Tumor	Invasive	Well circumscribed
Resectability	<25%	50–75%
Cirrhosis	90%	5%
AFP+	80%	5%
HepB+	65%	5%

AFP+, α-fetoprotein–positive; HCC, hepatocellular carcinoma; HepB+, hepatitis B–positive.

The most important pathologic issue is the distinct appearance and clinical behavior of the fibrolamellar variant of HCC. The contrast in clinical behavior is summarized in Table 33.5-2. On gross and radiologic inspection, fibrolamellar HCC is generally well demarcated and often encapsulated, with a central fibrotic area. It is a variant that generally occurs in young patients who lack underlying cirrhosis. α-Fetoprotein (AFP), which is commonly elevated in the usual case of HCC, is not elevated in fibrolamellar HCC. Other serum markers that often are elevated in fibrolamellar HCC include neurotensin[24] and vitamin B_{12} binding protein. The fibrolamellar variant of HCC is associated with a prolonged survival as compared with typical HCC, likely owing to the well-demarcated nature of the tumor and the greater range in treatment options for patients without underlying cirrhosis.[25]

HCC can also appear with mixed or combined features of HCC and cholangiocarcinoma. The two components of this tumor may be separate, adjacent to each other, or intimately mixed.[1,26] Biliary differentiation in HCC is associated with a poor prognosis, because such tumors are more rapidly growing and less vascular and, therefore, are more resistant to embolic therapy.[27] In the clear-cell variant of HCC, the cells have an abundant, pale, finely granular or vacuolated cytoplasm as a result of abundant glycogen, fat, or water. The prognostic importance of finding the clear-cell variant has been debated, but this subtype may be associated with a better prognosis.[28,29]

CLINICAL PRESENTATION

Even though it is generally a slow-growing tumor, the majority of HCCs present at an advanced stage, when most are beyond curative treatment. Because the liver is relatively hidden behind the right costal cartilages, tumors must reach substantial size before they are palpable. Furthermore, the large functional reserve of the liver masks any small impairment produced by local parenchymal disturbances. Therefore, small tumors are most often asymptomatic and are usually discovered during screening programs[30–32] or incidentally during imaging performed for other abdominal conditions.

Most cases of HCC are detected only when tumors are large, at a stage when local symptoms are common. Patients usually complain of a dull, right upper quadrant ache, sometimes referred to the shoulder. Hepatomegaly is a frequent accompa-

nying finding. The liver edge is hard and irregular, due both to tumor and the usual accompanying cirrhosis. A vascular bruit can be heard in approximately 25% of cases.[33] General symptoms of malignancy, including anorexia, nausea, lethargy, and weight loss, are common. The most common clinical presentation is the triad of right upper quadrant pain, mass, and weight loss.[34–36] Central necrosis of large tumors can also lead to fever, and HCC can present as pyrexia of unknown origin. For most patients, the presentation of HCC will also be the first presentation of the underlying cirrhosis. In one study, although 90% of patients were eventually found to have cirrhosis, fewer than 10% were thought, at first evaluation for HCC, to have chronic liver disease on the basis of history and clinical examination.[35]

Hepatic decompensation is another common presentation of HCC, with patients seeking medical attention owing to typical symptoms of liver failure such as ascites, jaundice, or encephalopathy. This decompensation of liver function is most often attributable to bulk replacement of functional parenchyma in a patient with previously compensated cirrhosis. HCC has a great propensity for vascular invasion and intravascular growth. Therefore, hepatic failure may also be due to portal vein occlusion secondary to intravascular tumor thrombus.[37–39] A much rarer cause of liver failure is Budd-Chiari syndrome, resulting from direct invasion and occlusion of the hepatic vein and inferior vena cava by tumor and tumor thrombus.

Gastrointestinal bleeding often complicates the clinical course of patients with HCC and, in 10% of patients, is the presenting finding.[39] In approximately one-half of these cases, bleeding is from esophageal varices,[39] which can result from portal hypertension due to cirrhosis alone or with an added contribution of intraportal thrombus. Patients with gastrointestinal bleeding from esophageal varices have an extraordinarily poor prognosis, with a median survival measurable in weeks.[38] The particularly poor prognosis of variceal bleeding complicating HCC is due to the common finding of intraportal thrombus, which further increases the portal pressure and makes control of bleeding varices more difficult. In fact, in one study, nearly one-fourth of patients with HCC died from massive variceal hemorrhage.[37] Gastrointestinal bleeding can occur from other causes as well, such as benign peptic ulcer or direct invasion of the gastrointestinal tract by tumor.[39]

The most dramatic presentation of HCC is tumor rupture, which is the initial presentation in 2% to 5% of patients with HCC.[40–45] Patients present with acute abdominal pain and swelling and are found to have, in addition to swelling, guarding, rebound tenderness, and ileus. Patients also commonly have signs of hemodynamic instability or overt hypovolemic shock. Diagnosis is confirmed by findings of either tumor mass or peritoneal blood through imaging, laparotomy, or paracentesis.[44,46,47]

Jaundice as a presenting symptom of HCC occurs in up to one-half of all patients. The most common cause of the jaundice is hepatic parenchymal insufficiency.[34,48–50] On rare occasions (<10% of jaundiced patients), jaundice associated with HCC results from biliary obstruction.[34,51–56] The biliary obstruction can occur from intraluminal tumor, from hemobilia, or from extraluminal bile duct obstruction. In the clinical evaluation of jaundice in a patient with HCC, it is enormously important to distinguish hepatocellular failure from obstruction. The former usually indicates that the patient is beyond any therapeutic benefit, whereas the latter can be treated, often with good palliation and even potential cure.[35,54,57–61]

Rarely (<5% of cases), HCC can present with paraneoplastic syndromes owing to hormonal or immune effects of the tumors.[62] The most important of these syndromes are hypoglycemia, erythrocytosis, hypercalcemia, and hypercholesterolemia. Porphyria cutanea tarda, virilization and feminization syndromes, carcinoid syndrome, hypertrophic osteoarthropathy, hyperthyroidism, and osteoporosis can also occur.[63–65]

DIAGNOSTIC INVESTIGATIONS

For patients suspected of suffering from HCC, the aims of diagnostic investigations are (1) verification of diagnosis, (2) determination of extent of disease, (3) determination of functional liver reserve, and (4) assessment of biologic determinants that affect long-term prognosis.

Verification of Diagnosis

Diagnosis of HCC can usually be positively established noninvasively by a combination of history, physical assessment, imaging, and blood tests. There is little diagnostic doubt in a patient with a liver mass consistent with an HCC visible on computed tomography (CT) or magnetic resonance imaging (MRI) and a serum AFP of more than 500 ng/dL. This combination is diagnostic, and treatment can be instituted without tissue diagnosis. The presence of cirrhosis or hepatitis infection, as documented by presence of HB_sAg or HCV virus in the blood, is further confirmation.

In the patient with a space-occupying lesion on ultrasonography (US) or CT and a nondiagnostic AFP level, the role of a percutaneous needle biopsy often is debated. There is no doubt that needle biopsy is diagnostic for HCC. However, complications are also not infrequent. Hemorrhage or tumor rupture can occur. Furthermore, there is also a small but finite risk of tumor spillage and seeding of the needle biopsy tract.[66] In cases of potentially resectable HCC, where the diagnostic certainty is high, we would proceed to surgical exploration without tumor biopsy. Indeed, in this clinical scenario, the histologic appearance of the nonneoplastic liver may have a greater impact on surgical planning. If advanced cirrhosis will preclude safe resection, we often perform a biopsy the portion of the liver that does not contain tumor, for histologic evaluation.

In patients with a nondiagnostic AFP level who are not surgical candidates and, therefore, are not candidates for curative therapy, tumor biopsy is performed if the patients are candidates for palliative therapy. In that case, fine-needle aspiration for cytologic evaluation is usually performed in preference to core-needle biopsy for histology, as comparative studies indicate that smear cytology yielded a much higher percentage of correct diagnoses as compared to microhistology (86% vs. 66%).[67] Patients who are not candidates for palliative therapy do not need a definitive diagnosis, and biopsy is discouraged.

Determination of Extent of Disease

The two issues to be resolved by the extent-of-disease evaluation are whether the disease is isolated to the liver and whether distribution of tumor in the liver is amenable to surgical excision. The most common sites of metastases of HCC include lung, peritoneum, adrenal gland, and bone. Hence, chest radiography is mandatory. Cross-sectional imaging, such as CT or

RI. of the abdomen should be scrutinized for peritoneal and lrenal sites of disease. Many centers consider bone scans andatory prior to liver resection. Certainly, in patients with in attributable to bony metastases, a bone scan should be :rformed. A finding of extrahepatic disease changes the prog- sis of the patients greatly, as such a finding precludes the ssibility of hepatectomy as curative therapy.

The extent of liver involvement usually is determined by CT nning. This diagnostic imaging modality is widely available d relatively inexpensive. In interpreting any cross-sectional aging modality for the patient with HCC, the number and tribution of liver tumors must be determined, as well as the gree of vascular invasion. In this regard, triple-phase (non–ntrast-enhanced, arterial phase, and portal phase) CT images ould be obtained. HCCs are generally highly vascular tumors, d tumors on images with contrast enhancement may become dense with the surrounding liver. Tumors sometimes are visi- only during the non–contrast-enhanced phase. Because C has a great propensity for vascular invasion and extension, nor thrombus in the portal vein, hepatic vein, or vena cava is t unusual. Scans should therefore be scrutinized for evidence such invasion, as therapy and prognosis can be altered signif- ntly by such findings. If such invasion is suspected but not wen by CT, Doppler US or MRI is indicated.

At some centers, hepatic angiography is standard.[68,69] Some e even advocated routine use of iodized oil (Lipiodol) cted angiographically to delineate hepatic extent of disease ther.[70] This lipid is preferentially retained in HCC because of particle size. These angiographic methods are highly sensitive the presence of tumor. Nonetheless, with current helical CT MRI, there is only minor incremental yield. We rely on angio- phy only when we suspect small tumors not visible by conven- al cross-sectional imaging, such as for a patient with small ounts of disease seen on CT who has a very high AFP level.

sessment of the Patient's General Condition and patic Functional Reserve

he evaluation of patients for possible hepatectomy, cardio- monary assessment should be conducted as for any major cedure. Patients older than 65 years or patients with a his- r or symptoms consistent with cardiopulmonary disease uld be referred for formal medical preoperative evaluation. Assessment of baseline liver function and assessment of plications of cirrhosis are paramount in the process of rmining the optimal treatment option for each patient. overy from liver resection is reliant on the capacity of the r to regenerate. The cirrhotic liver often has a reduced acity for regeneration. In addition, cirrhosis and portal ertension often are associated with derangements in atic production of coagulation factors and with thrombocy- enia, which explains the increased risk of liver failure and ding after resection for HCC. Indeed, the complication after ablative therapies is increased proportionate to the ree of liver dysfunction.[71,72] Consequently, many clinical laboratory methods have been devised for determining the l of risk for various therapies.

ERUM LIVER FUNCTION TESTS AND CLINICAL ESSMENT. Various liver function tests, alone or in combina- , have been touted as useful for predicting risks of liver resec-

TABLE 33.5-3. Pugh's Modification of Child's Grading of Cirrhosis

Measurement	*1 Point*	*2 Points*	*3 Points*
Bilirubin (mg/dL)	1–1.9	2–2.9	>2.9
Prothrombin time prolongation (sec)	1–3	4–6	>6
Albumin (g/dL)	>3.5	2.8–3.4	<2.8
Ascites	None	Mild	Moderate to severe
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4

Note: Pugh-Child's grade A, 5–6 points; B, 7–9 points; C, 10–15 points.

tion and other treatments for HCC. Various single serum measures of liver function have been suggested to be useful predictors of perioperative outcome, including serum bilirubin[73] and serum alanine aminotransferase.[74] A doubling of bilirubin has been suggested as a contraindication for liver resection.[73] Other investigators have deemed a platelet count of fewer than 50,000 or a prolonged prothrombin time (>4 seconds over control) as a relative contraindication for hepatic resection.[75] Most investigators, however, have not relied on a single parameter but rather have used a combination of clinical and biochemical parameters to gauge safety of hepatectomy and other treatments. In this regard, the most clinically useful system is the Pugh-Child's classification, which is a point-scoring system for evaluation of liver function based on the levels of serum bilirubin, coagulation profile, serum albumin, presence or absence of ascites and encephalopathy, and nutritional status (Table 33.5-3).[76,77] Functionally well-compensated cirrhosis is classified as Pugh-Child's classification grade A; decompensating cirrhosis is grade B; and decompensated cirrhosis is grade C. Generally, partial hepatectomy is offered only to patients who are Pugh-Child's grade A and to the most favorable grade B patients.[78] In general, Pugh-Child's grade C patients are offered only supportive care, as even nonsurgical ablative methods, such as embolization, are associated with procedure-related mortality in one-third of patients.[71]

DYNAMIC TESTS. Many sophisticated dynamic measures of liver function have also been used in attempts to quantitate hepatic function. Investigators have attempted to use elimination of certain dyes that are exclusively cleared by the liver, such as bromsulfophthalein or indocyanine green, as measures of hepatic function. Galactose clearance or [^{14}C]aminopyrine clearance has also been used to evaluate the specific metabolic capacity of the liver. Of these, the most commonly used evaluative modalities in clinical practice are indocyanine green retention at 15 minutes[79] and the [^{14}C]aminopyrine breath test,[80] though controversy still exists concerning their usefulness.[81] We do not use these tests on a routine basis in our care of the patient with HCC but have found the clinical Pugh-Child's classification sufficiently discriminatory for selecting patients for therapies.

PORTAL PRESSURES AND BLOOD FLOW. Another relatively simple test that may be predictive of perioperative outcome is the hepatic venous wedge pressure. By passing a venous catheter through the vena cava into the hepatic vein, the hepatic venous pressure can be directly ascertained. By balloon occlusion of the hepatic vein, the hepatic venous wedge pressure, which is a reflec-

TABLE 33.5-4. Treatment Options for Hepatocellular Carcinoma

POTENTIALLY CURATIVE OPTIONS
Partial hepatectomy
Total hepatectomy with orthotopic liver transplantation
PALLIATIVE TREATMENTS
Regional therapies
Ablative therapies: cytoreductive therapies
Palliative resection
Cryosurgery
Microwave ablation
Ethanol injection
Acetic acid injection
Hepatic artery transcatheter treatments
Transarterial chemotherapy
Transarterial embolization
Transarterial chemoembolization
Transarterial radioembolization
^{90}Y microspheres
Lipiodol ^{131}I
Conformal radiation
Systemic therapies
Chemotherapy
Immunotherapy
Hormonal therapy
SUPPORTIVE CARE

tion of the portal pressure, can be determined. These measurements have been touted as useful in segregating Pugh-Child's grade B patients who may have favorable results from resection from those likely to experience major complications.[82]

POTENTIALLY CURATIVE TREATMENTS

Therapies for HCC can be separated into resection, ablation, radiotherapy, systemic chemotherapy or immunotherapy, and supportive care (Table 33.5-4). Resectional therapy represents the only potentially curative option.

Partial Hepatectomy

Partial hepatectomy represents the most common procedure for treatment of HCC performed with curative intent. The liver is normally a very resilient organ with remarkable regenerative capacity. In a noncirrhotic liver, routine recovery can be expected even after resection of more than two-thirds of the functional parenchyma.[83] In the United States, nearly one-half the patients with HCC will have no associated cirrhosis.[84] For patients with no cirrhosis, operative mortality at most major centers is generally less than 5%, and very extensive procedures are justified by the low risk and the potential for long-term survival and cure. Resection is associated with a 5-year survival in more than 30% of patients.[85–89] For a patient without cirrhosis, partial hepatectomy is a relatively safe procedure and is the treatment of choice for eradication of HCC (Table 33.5-5).

Worldwide, however, most cases of HCC are associated with cirrhosis, which greatly increases the risk for partial hepatectomy (see Table 33.5-5). This increase in risk is due in part to intraoperative factors. These patients will usually have rigid and hard parenchyma and established varices that are difficult to manipulate and are prone to bleeding. In addition, such patients will have thrombocytopenia and coagulation defects that further exacerbate the risk of hemorrhage. Postoperatively, the liver may not regenerate, resulting in liver failure. Furthermore, postoperative exaggeration of portal hypertension may lead to ascites and variceal bleeds. It is understandable, therefore, that resection is associated with increased morbidity and mortality in these patients. Even for a cirrhotic patient with well-compensated liver function, we are reluctant to remove more than 20% to 25% of the functional parenchyma.[81,89–92] Until recently, even at centers with a low mortality for partial hepatectomy in the noncirrhotic population, partial hepatectomy for patients with cirrhosis was associated with a 10% mortality or higher (see Table 33.5-5).[85,86,93–95] This explains the nihilistic view adopted by some for this disease, as well as the interest in treating this disease by total hepatectomy and liver transplantation. Nevertheless, even now, cirrhotic patients who survive the operation have a 5-year survival of approximately 30% (Table 33.5-6).[85–89,93–95] Over the last decade, a number of series have demonstrated increasing safety of partial hepatectomy in cirrhotic patients (see Table 33.5-5). The mortality at most major centers treating HCC has been reduced to the 5% level, owing to improvements in patient selection, perioperative support, and surgical technique.[84,96–98]

Patient selection for surgery depends first and foremost on hepatic function. As discussed earlier, in Serum Liver Function Tests and Clinical Assessment, the most commonly used clinical selection criteria for patient's fitness for surgery relies on the Pugh-Child's score. Few surgeons are willing to perform hepatic resection for patients with a Pugh-Child's grade C liver status. Most surgeons will consider resection only for patients with Pugh-Child's grade A liver functional reserve and the best Pugh-Child's grade B patients.

The major changes in operative conduct that have improved perioperative outcome include a willingness to use inflow occlusion during resection and a willingness to accept nonanatomic resection. Temporary occlusion of the hepatic artery and portal vein during liver resection by clamping the gastrohepatic ligament has been a useful technique for reducing blood loss during hepatectomy for patients with no cirrhosis.[99] In the past, surgeons have been reluctant to use such inflow occlusion, called the *Pringle maneuver*, in cirrhotic patients because of fears that cirrhotic parenchyma will not tolerate the transient ischemia. Recent studies have indicated that the reluctance to use this technique was largely unfounded and that cirrhotic liver can tolerate a Pringle maneuver for more than 30 minutes.[100,101] The most important change in operative technique, however, is a willingness to use limited, nonanatomic resections. For patients with no cirrhosis, most major centers adhere to the anatomic boundaries of the various segments during liver resection for cancer. Lobectomies, sectorectomies, and segmentectomies are preferred over wedge and other nonanatomic resections because limited resections are more likely to result in a positive microscopical margin.[102] In the cirrhotic liver, however, a smaller resection margin is acceptable if it will reduce the chance of postoperative liver failure. The smallest resection that will remove all gross tumor is generally used at most centers.

TABLE 33.5-5. Operative Mortality as Related to Liver Cirrhosis

Study	No. of Cases	Cirrhosis (%)	Mortality (%)	Comments
Noncirrhotic patients				
Mnegchao et al., 1980[85]	55	0	2	—
Tsuzuki et al., 1990[86]	39	0	3	—
Chen et al., 1989[87]	65	0	2	—
Bagasue et al., 1993[88]	52	0	6	—
Vauthey et al., 1995[89]	70	0	1	—
Bismuth et al., 1995[503]	68	0	3	—
Mixed patients				
Kishi et al., 1983[504]	57	39.4	11	—
Lee et al., 1986[505]	109	40.4	3	—
Kanematsu et al., 1988[506]	121	80	12	—
Lai et al., 1991[507]	39	84.6	8	Small HCC
Nagasue et al., 1993[91]	229	77	7	—
Hemming et al., 1993[79,508]	50	26	0.5	Segmental resection
Fan et al., 1994[509]	124	81.5	11	—
Chen et al., 1994[510]	205	49.8	4	Large HCC
Lai et al., 1995[511]	149	69	22	Before 1987
	128	78	15	1987–1991
	66	74	6	1992–1995
Kawasaki et al., 1995[98]	112	67.9	1	—
Takenaka et al., 1996[512]	280	52	2	—
Nadig et al., 1997[513]	71	24	21	—
Cirrhotic patients				
Liver Study Group of Japan, 1980[93]	153	100	30	—
Nagao et al., 1987[94]	72	100	19	—
Mnegchao et al., 1980[85]	126	100	12	—
Kanematsu et al., 1984[95]	50	100	12	—
Franco et al., 1990[514]	72	100	7	—
Tsuzuki et al., 1990[86]	119	100	13	—
Chen et al., 1989[87]	55	100	7	—
Bagasue et al., 1993[88]	177	100	12	—
Capussotti et al., 1994[97]	33	100	6	—
Vauthey et al., 1995[89]	30	100	14	—
Fuster et al., 1996[96]	48	100	4	—

HCC, hepatocellular carcinoma.

As safety of resections has improved, reports of increasingly large experiences in the treatment of HCC provide long-term results that allow for analysis of prognostic factors that influence long-term outcome. Many factors that previously were thought to be contraindications to surgical resection have not been substantiated by data. It is now clear that multiple lesions do not preclude surgical resection[88,89]: Five-year survival in patients resected of multiple tumors is expected to be between 24%[89] and 28%.[88] Presentation with intraductal tumor and obstructive jaundice also does not preclude long-term survival after surgical resection.[86] Therefore, distinguishing biliary obstruction from hepatic insufficiency as the cause for jaundice is very important in a patient who presents with HCC and jaundice. Finally, synchronous direct invasion of adjacent organs such as the diaphragm by HCC is not an absolute contraindication to resectional surgery.[103,104]

One group that has a particularly poor prognosis is patients with major intravascular extension of tumor. Even though tumor thrombus can be treated with liver resection and thrombus extraction, the risk of disseminated disease is extremely high in these patients.[105] If the tumor thrombus involves the vena cava or main portal vein, liver resections accompanied by venous tumor thrombectomies are unlikely to result in long-term survival.

Neoadjuvant Treatment of Tumors

Many groups have attempted to treat HCC with local or systemic therapies prior to attempts at surgical resection. The rationale for such neoadjuvant therapies is that large primary tumors may be sufficiently reduced in bulk to make resection safer and that local and systemic microscopic disease may be reduced or eradicated, thereby improving long-term outcome. In this regard, methods that have been employed to achieve these goals include transarterial chemoembolization,[106,107] combined chemotherapy [doxorubicin (Adriamycin) and 5-fluorouracil (5-FU)] and radiotherapy (2100 cGy),[108] hepatic artery infusion of chemotherapeutic agents, radioimmunotherapy, fractionated regional radiotherapy,[108] and transarterial ^{90}Y microspheres.[109]

TABLE 33.5-6. Survival Rates after Liver Resection for Hepatocellular Carcinoma

Study	No. of Cases	Survival (%)					Comments
		1-Y	2-Y	3-Y	5-Y	10-Y	
Kanematsu et al., 1984[95]	37	80	60	—	33	—	Limited resection
	13	79	68	—	23	—	Major resection
Okuda et al., 1984[516]	98	62	43	34	—	—	—
Hsu et al., 1985[517]	49	96	91	—	—	—	HCC <5 cm
	49	63	51	—	—	—	HCC >5 cm
Lee et al., 1986[505]	109	84	72	—	—	—	—
Nagao et al., 1987[94]	94	58	—	33	20	—	—
Kanematsu et al., 1988[506]	107	83	—	51	26	—	—
Franco et al., 1990[514]	72	68	55	51	—	—	100% cirrhosis
Yamamoka et al., 1990[519]	295	76	—	44	31	—	—
LCSG, Japan 1990[93]	2174	67	—	40	29	—	—
Ringe et al., 1991[521]	131	68	54	42	36	—	—
Lai et al., 1991[507]	39	59	—	28	11	—	HCC <5 cm
Sasaki et al., 1992[522]	186	—	—	—	44	—	Cirrhotic
	57	—	—	—	68	—	Noncirrhotic
Nagasue et al., 1993[91]	229	80	—	51.3	26	19	—
Ouchi et al., 1993[523]	47	89	—	65	43	—	—
Takenaka et al., 1994[524]	229	89	—	76	76	—	<70 y
	39	87	—	70	52	—	>70 y
Suenaga et al., 1994[525]	134	100	—	88	68	—	—
Capussotti et al., 1994[97]	33	66	43	37	—	—	Large HCC
Bismuth et al., 1995[503]	68	74	—	52	40	26	Noncirrhotic
Lai et al., 1995[511]	343	60	—	33	24	—	1987–1991
Vauthey et al., 1995[89]	106	—	—	—	41	—	—
Kawasaki et al., 1995[98]	112	92	—	79	—	—	—
Fuster et al., 1996[96]	48	—	—	64	—	—	—
Takenaka et al., 1996[512]	280	88	—	70	50	—	—
Nadig et al., 1997[513]	71	—	—	—	20	—	—
Fong et al., 1999[84]	154	80	—	51	39	—	67% cirrhosis

HCC, hepatocellular carcinoma; LCSG, Liver Cancer Study Group.

Another form of preoperative treatment is immunoembolization. Neoadjuvant transarterial immmunoembolization (TIE) was tested with OK-432, a *Streptococcus* preparation. In a comparison of 22 patients who underwent TIE versus transarterial embolization (TAE) alone, the 1- and 2-year disease-free survival rates after resection were 85% and 85% for TIE and 62% and 56% for TAE, respectively.[110] Lygidakis and Tsiliakos[111] randomized 91 patients with HCC to

chemotherapy as adjuvant therapy after resection will improve long-term outcome await prospective studies. Overall, though, each of these studies consisted of only a few patients and, though such neoadjuvant therapy seems promising, a definitive role for any of these treatments in a neoadjuvant setting has not been unequivocally demonstrated.

An alterative neoadjuvant approach that attempts to

In a study from China, 61 patients with resected HCC were randomized to no further therapy or postoperative hepatic infusion of Lipiodol and cisplatin with systemic epirubicin. The treated group seemed to have a higher extrahepatic recurrence and a worse outcome.[118] Another study of 57 patients with resected HCC randomized to hepatic arterial infusion and systemic epirubicin versus no further treatment again demonstrated no difference in overall and disease-free survival.[119]

Though transarterial chemoembolization is used extensively for the treatment of unresectable disease, randomized studies have not supported the use of this modality in the adjuvant setting. In fact, in three different studies, survival has been worse for those treated with chemoembolization after resection.[120–122] To date, no study has demonstrated that any systemic chemotherapy or immunotherapy improves survival after hepatectomy for HCC.

Two positive randomized trials of adjuvant therapy after resection for HCC have been reported. The first involves the use of the retinoid derivative polyprenoic acid, which had been shown to inhibit hepatocarcinogenesis in rodents.[123] In a study randomizing patients, after curative resection or PEI for HCC, to receiving either polyprenoic acid or placebo, significantly higher numbers of patients receiving placebo developed additional HCC. Currently, polyprenoic acid is not available in the United States, but these data encourage further study of this and other retinoid derivatives in adjuvant treatment for HCC and in chemoprevention for patients at high risk for developing HCC.

The other positive adjuvant study involved the use of radioembolization employing transarterial delivery of ^{131}I-labeled Lipiodol. This compound has demonstrated significant activity against small HCCs, but problems with dosimetry have limited its use for patients with bulky unresectable disease. In a prospective, randomized study, Lau et al.[124] compared 21 patients who received 50 mCi of transarterial ^{131}I-Lipiodol within 6 weeks of liver resection for HCC with 22 patients receiving no adjuvant therapy. The 3-year survival rates for the treated group and the control group were 85% and 46%, respectively. These results await multicenter studies to confirm with bigger numbers not only the long-term cancer results but also the feasibility of using such radioembolization methods in diverse centers.

Total Hepatectomy and Liver Transplantation

From a theoretic standpoint, total hepatectomy and liver transplantation is the most attractive treatment for HCC. This treatment allows for removal of the liver cancer with the widest margin possible. It also allows for removal of diseased parenchyma that may contain microscopic metastatic disease as well as parenchyma that may be predisposed to formation of second primary tumors. A number of studies have attempted to define the biologic parameters predicting good long-term outcome after liver transplantation. The best results are seen in patients with fibrolamellar histology and in patients with small incidental tumors found unexpectedly within the explanted liver. Characteristics associated with poor long-term outcome include advanced stage, the presence of a margin involved by tumor, large tumors, multiple tumors, microscopic or macroscopic vascular invasion, and bilobar disease.[125,126] Patients with tumors smaller than 5 cm have a mean survival of 55 months, whereas those with tumors larger than 5 cm have a mean survival of only 24 months.[127,128] Therefore, most transplantation centers will not consider patients with tumors larger than 5 cm for transplantation. Currently, at most centers, only patients with fewer than three tumors, all smaller than 5 cm, and with no main portal vein or vena caval involvement are considered for liver transplantation.

TABLE 33.5-7. Results of Liver Transplantation for Hepatocellular Carcinoma

Study	No. of Cases	Operative Mortality (%)	Survival (%) 1-Y	3-Y	5-Y
O'Grady et al., 1988[129]	50	28	40	—	—
Ringe et al., 1989[526]	52	15	—	37	—
Yokoyama et al., 1990[127]	80	13	64	45	45
Iwatsuki et al., 1991[527]	71	NR	—	48	—
Pichlmayr et al., 1992[528]	87	24	—	—	20
Haug et al., 1992[128]	24	17	71	42	—
Moreno-Gonzalez et al., 1992[529]	12	0	80	16	—
Bismuth et al., 1993[530]	60	5	—	49	—
Romani et al., 1994[531]	27	11	82	71	—
Chung et al., 1994[532]	29	14	61	46	—
Dalgic et al., 1994[533]	39	NR	56	32	26
Farmer et al., 1994[139]	44	17	71	42	—
Tan et al., 1995[132]	15	7	—	63	—
Selby et al., 1995[125]	105	NR	66	39	36
Pichlmayr et al., 1995[528]	36	19	57	31	27
Schwartz et al., 1995[130]	57	0	72	57	—
Mazzaferro et al., 1996[131]	48	6%	75 at 4 y	—	—

NR, not reported.

In clinical practice, however, biology of the cancer is not the most important determinant of the usefulness of transplantation. Liver transplantation is associated with substantial morbidity and mortality (Table 33.5-7). Series from the 1980s and early 1990s often report mortality rates as high as 10% to 20%.[129] Though some recent series have reported much-improved perioperative mortality (see Table 33.5-7),[130–132] the morbidity is still substantial. In patients with liver dysfunction in either the Pugh-Child's grade B or C categories, however, total hepatectomy with liver transplantation represents the only potentially curative option.

The greatest obstacle is the limited availability of livers for transplantation. Even in the United States, where active public campaigns have resulted in comparatively high rates of organ donations for transplantation, only 3000 to 4000 livers are available each year. This would explain the limited numbers of livers used in transplantation for treatment of liver cancers. Only approximately 100 transplantations are performed each year for this indication (Fig. 33.5-1). In countries in the Far East, where organ donation goes against social and religious beliefs, the shortage of donated organs is even greater. Living-relative liver transplants offer a potential source of organs for such use.[133,134] However, the morbidity associated with donation of a lobe of liver is substantial, and mortality is not only a

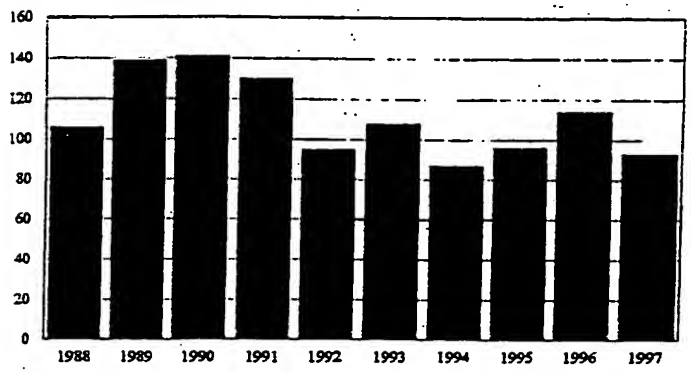

FIGURE 33.5-1. Number of liver transplantations performed each year in the United States for cancer. Use of liver transplantation for this indication is greatly limited by the shortage of organs. (Data from UNOS.)

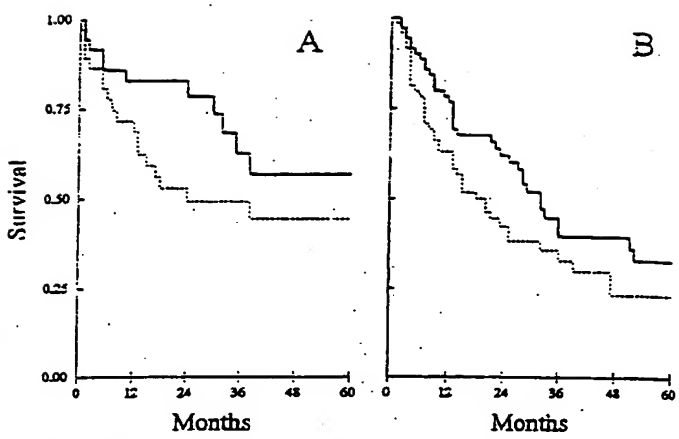

FIGURE 33.5-2. Survival (*solid line*) and disease-free survival (*dotted line*) after resection of (A) small (<5 cm) or (B) large (>10 cm) hepatocellular carcinoma. Results of resection for these small tumors are highly favorable and comparable to liver transplantation. (From ref. 84, with permission.)

theoretic but a documented actual complication. For patients with cancer, the likelihood of recurrence brings into question the ethics of endangering a donor's life.

In addition, the costs of liver transplantation are substantial. Certainly, it is much more cost-effective to use available livers for the treatment of benign diseases. In many parts of the world, however, the high costs completely rule out transplantation for any indication. Because of these obstacles, liver transplantation is not likely to make an important impact on the worldwide treatment of cancer in the near future.

Comparing results of partial hepatectomy with results of liver transplantation for HCC has been difficult, primarily because patients with very distinct clinical characteristics are usually selected for each treatment. Patients selected for partial hepatectomy generally have good liver function and may have enormous tumors. Patients selected for transplantation almost always have small tumors but may have advanced liver failure. In the past, the reported 1-, 3-, and 5-year survival rates of liver transplantation for HCC were 40% to 82%, 16% to 71%, and 19.6% to 36%, respectively, rates that were highly comparable to those achieved with partial hepatectomy (see Table 33.5-7). This indicated not so much that these two techniques were equivalent as that the right patients were being selected for each treatment.

Recently, two series of studies have encouraged a renewed comparison of these two treatment options. In a series from the transplantation literature, operative mortality appears to have been dramatically reduced to a current low of less than 5%.[126,130–132] With such low operative mortality, Mazzaferro et al.[131] are reporting 3-year survival after transplantation of 85% for small HCC. This has fueled enthusiasm for liver transplantation in this clinical setting. At the same time, a number of articles examining partial hepatectomy for HCC have been published that include sufficient data in the subset of patients with small tumors to allow comparison.[84,135] It appears that partial hepatectomy for patients with small tumors also results in very favorable outcomes. For a patient with a tumor that is less than 5 cm in diameter, the 5-year survival can be expected to be 45% to 57%.[84,135,136] In fact, disease-free survival can be expected in 44% of patients (Fig. 33.5-2).[84] These results are comparable to the best results for liver transplantation. Therefore, given the organ shortage and costs of liver transplantation, partial hepatectomy should still be regarded as the curative treatment of choice. For patients without cirrhosis or with Pugh-Child's grade A cirrhosis, partial hepatectomy should be considered first. Total hepatectomy with transplantation may be necessary in this group if removal of tumor requires extensive resection of nonneoplastic liver. For patients with severe liver dysfunction, total hepatectomy and transplantation is a better option and may be the only viable option.

Because the incidence of recurrence of HCC after liver transplantation is high, many investigators have attempted to improve long-term results by use of adjuvant therapies. Cherqui et al.[137] used an adjuvant regimen combining neoadjuvant chemoembolization and radiotherapy with posttransplantation chemotherapy. Stone et al.[138] used a regimen of aggressive neoadjuvant, intraoperative, and postoperative chemotherapy. Farmer et al.[139] used an adjuvant chemotherapeutic regimen combining 5-FU, cisplatin, and doxorubicin. These are all small studies based on a sound understanding of HCC and represent promising approaches. All use neoadjuvant therapy because patients often spend a considerable amount of time awaiting availability of a liver for transplantation. However, given the small number of transplantations performed yearly for HCC, the role, timing, and regimens to be used are far from decided.

PALLIATIVE TREATMENT MODALITIES

Most patients presenting with HCC will have disease that is not treatable by partial hepatectomy. Even if the disease is confined to the liver, the likelihood of treatment with total hepatectomy and transplantation is low for reasons outlined in the preceding section, Total Hepatectomy and Liver Transplantation. Nevertheless, if the disease is confined completely or largely to the liver, local tumor ablative therapies can be performed and result in good local control of disease. The ablative methods with the longest track record include ethanol injection, embolization, and cryotherapy. These will be discussed with specific emphasis on technical limitations, morbidity, and their likely role in patient clinical management. Other more investigative modalities, such as radiotherapy, radiofrequency ablation, and laser heat ablation, also are discussed.

TABLE 33.5-8. Systemic Chemotherapy for Hepatocellular Carcinoma

Study	No.	Treatment	Partial Response (%)	Stable Disease (%)
Leung[534]	50	Cisplatin, doxorubicin, 5-FU + IFN	13 (26)	10 (20)
O'Reilly[535]	7	CPT-11	1	2 (29)
Umsawasdi[536]	13	5-FU, mitomycin C	5 (38)	NR
Vogel[537]	41	Doxorubicin	7 (17)	9 (29)
Baker[538]	38	Doxorubicin + 5-FU	5 (13)	NR
Ravey[539]	26	Doxorubicin + bleomycin	5 (19)	8 (31)
Okada[540]	27	Cisplatin, mitoxantrone, CI + 5-FU	9 (33)	16 (59)
Pan[113]	20	Cisplatin, doxorubicin, 5-FU + IFN	2 (10)	10 (50)
Zanibone[541]	14	Vitamin K	0	4 (29)
Noy[542]	20	FUDR, doxorubicin + IFN	4 (10)	NR
Benson[543]	25	Eniluracil + 5-FU	0	6 (24)
Cheng[168]	33	Etoposide + tamoxifen	8 (24)	NS
Bobbio-Pallavicini[169]	36	Epirubicin + etoposide	14 (39)	11 (30)
Strumberg[544]	16	Paclitaxel	1 (6)	9 (56)
Chao[545]	20	Paclitaxel	0	5 (25)
Stuart[546]	10	5-FU + IFN	0	NR
Mani[547]	16	UFT + LV	0	3 (19)
Gebbia[548]	50	5-FU + LV + hydroxyurea	5 (10)	15 (30)
Chlebowski[549]	157	Doxorubicin	17 (11)	NR
Falkson[550]	25	Neocarzinostatin	2 (8)	NR
Melia[551]	44	VP-16	7 (16)	NR
Falkson[552]	35	Cisplatin	6 (17)	NR
Ji[553]	30	Cisplatin + IFN	4 (13)	NR
Falkson[552]	35	Mitoxantrone	0	NR

CI, continuous infusion; CPT-11, irinotecan; 5-FU, 5-fluorouracil; FUDR, fluorouridine; IFN, interferon; NR, not reported; NS, not significant; LV, leucovorin; UFT, uracil + tegafur; VP-16, etoposide.

Systemic Therapies

When a patient has widely disseminated disease, only systemic therapies make sense. However, the results of chemotherapeutic therapy or other systemic therapies for HCC have been dismal.

SYSTEMIC CHEMOTHERAPY. Numerous chemotherapeutic regimens have been tested for use against HCC (Table 33.5-8). HCC is, however, highly resistant to chemotherapy, owing to multiple factors: Tissue analysis has revealed that HCC harbors high levels of dehydropyrimidine dehydronase (DPD), and it is known that cells high in DPD are generally resistant to 5-FU.[140] In addition, HCC exhibits overexpression of the MDR1 (multidrug resistance) gene[141,142] and the gene product P glycoprotein.[141] This would explain the modest effects of 5-FU on HCC. In an Eastern Cooperative Oncology Group (ECOG) study of eniluracil (a DPD inhibitor) and 5-FU, 5 of 35 patients with HCC developed stable disease but no responses.

Doxorubicin is the most popular drug studied, though published data from 13 studies indicate that administration of this drug either alone or in combinations results in less than a 20% response and a median survival of less than 4 months.[143,144] Response to either single agent or multiagent systemic chemotherapy occurs in only 10% to 20% of patients (see Table 33.5-8). Furthermore, even the objective responses are short-lasting. In a systemic review[145] and metaanalysis[146] of the published randomized studies on HCC, neither doxorubicin nor any chemotherapeutic agent used singly or in combination has been shown to have any survival benefit for HCC patients. It is generally acknowledged that systemic chemotherapy has minimal impact on survival of patients with this disease. At our institution, systemic chemotherapy is offered mostly in the context of clinical trials. Moreover, most patients with unresectable disease are jaundiced or have a poor performance status because of extensive liver disease, making use of chemotherapeutic drugs virtually impossible.

HEPATIC ARTERIAL INFUSION. Because the results with systemic chemotherapy are far from optimal, regional delivery of chemotherapy has been attempted. Such regional approaches rely on the dual nutrient blood supply of the liver, portal vein, and hepatic artery. Hepatic tumors, however, derive their blood supply mainly from the hepatic artery.[147,148] Infusion of chemotherapy directly into the hepatic artery may allow increased effective dose at the tumor with fewer systemic side effects.

Hepatic arterial infusion (HAI) chemotherapy can be accomplished through a percutaneously placed angiographic catheter, through an implantable arterial port inserted at open operation and connected to an external infusion pump, or using self-contained subcutaneous infusion pumps implanted at surgery. Drugs with high liver extraction rates and short plasma half-lives are particularly well suited for HAI chemotherapy.[149] The fluoropyrimidines [5-FU and 5-fluorodeoxyuridine (5-FUDR)], cisplatin, doxorubicin, and 4'-epidoxorubicin are chemotherapeutic agents that have been tested in this mode of delivery.

TABLE 33.5-9. Hepatic Arterial Chemotherapy for Hepatocellular Carcinoma and Other Hepatobiliary Tumors

Study	*No.*	*Treatment*	*PR (%)*
Ansfield, 1971[554]	11	5-FU	27
Misra, 1977[555]	13	5-FU, mitomycin C	69
Kinami, 1978[556]	14	Mitomycin C	50
Wellwood, 1979[557]	28	FUDR	54
Olweny, 1980[558]	10	Doxorubicin	60
Cheng, 1982[559]	16	Cisplatin	19
Urist and Balch, 1984[560]	13	Doxorubicin	47
Shildt, 1984[561]	30	FUDR, doxorubicin, streptozotocin	10
Ariq, 1992[153]	10	FUDR, mitomycin C, IFN	50
Patt, 1994[151]	29	FUDR, leucovorin, doxorubicin, cisplatin	41
Carr, 1998[562]	26	Cisplatin	42
Urabe, 1998[563]	15	Methotrexate, 5-FU, cisplatin, IFN	47
Okuda, 1999[194]	31	Cisplatin, 5-FU	29

5-FU, 5-fluorouracil; FUDR, fluorouridine; IFN, interferon; PR, partial response.

Most data for treatment of HCC by HAI chemotherapy are gleaned from various phase II clinical trials (Table 33.5-9). Intraarterial doxorubicin seems to be more active than intravenous treatment.[150,151] The highest response rates have been obtained with the drug FUDR. This drug has a high hepatic extraction ratio and short serum half-life, making it ideal for regional therapy. Warren et al.[152] reported a response rate of 60% in 15 patients. Ariq et al.[153] reported a 50% response rate in ten patients using an HAI regimen of mitomycin C, FUDR, and subcutaneous IFN. Makela and Kairaluoma[154] reported a 48% response rate with HAI mitomycin, with a median survival of 14 months. HAI of cisplatin has produced responses between 20% and 40%. In a small study comparing HAI of doxorubicin with systemic administration of doxorubicin, the response rate was greatly increased with HAI.[155]

Though th

a slightly longer 1-year but shorter 2-year survival was found the patients treated with IFN-β.[156] These modest results c tainly do not support the use of IFN as a single agent. Furth more, all these studies used relatively high doses of IFN, a therefore toxicities requiring dose reduction were not uncc mon.

Most current studies of immunotherapies, therefo involve use of lower doses of IFN in combination with chen therapeutic agents. The most promising combination is a re men of cisplatin, doxorubicin, 5-FU, and IFN-α. Using t combination, Leung and Lau[112] achieved a partial respor rate of 26% in 50 patients with unresectable HCC. Six of the patients experienced sufficient regression of tumor to all subsequent surgical resection. Two of these six patients had complete response as confirmed by pathologic analysis. Tl regimen incites significant toxicity, as demonstrated by a 4 treatment-related mortality.[112] Future randomized multicent trials must be performed to define completely the clinical rc for this regimen.

SYSTEMIC HORMONAL THERAPY. HCC has long bee observed to be more common in men. Subsequently, it w noted that these tumors also express receptors for estroge and androgens.[159] Therefore, hormonal manipulation h been the basis of a number of trials directed at HCC. Of th antiestrogen compounds, tamoxifen has undergone the mo extensive testing. This drug inhibits growth of HCC *in vitr* The mechanisms of action against HCC, however, may not b related to its antiestrogen effects. Hepatocellular tumo express a high level of the MDR gene product P glycopr tein.[160] Tamoxifen is a potential MDR-reversing agent.[1 Overall, results of clinical trials using tamoxifen have bee mixed. Three small, randomized studies comparing tamo ifen to no treatment or placebo showed that tamoxifen signi icantly prolonged survival.[162-164] A large study involving 12 patients showed no benefit of tamoxifen over placebo i terms of tumor progression or survival.[165,166] Another recer randomized study of 496 patients with HCC showed no diffe ence in survival in patients receiving tamoxifen or no tamo

Ablative Therapies

PERCUTANEOUS ETHANOL INJECTION. Percutaneous ethanol injection (PEI) was first advocated by Sugiura[171a] in 1983 for ablation of liver tumors. Tumor cells are killed by a combination of cellular dehydration, coagulative necrosis, and vascular thrombosis. Direct injections can be easily performed during open surgery or laparoscopy or percutaneously using ultrasound guidance. This ablative procedure is most often performed percutaneously and is very effective and safe for treating small HCCs. Ethanol injections are usually very well tolerated by patients, side effects being primarily pain, fever, and a transient rise in liver enzymes. Though other side effects, including bleeding, tumor rupture, needle tract tumor implantation,[172] and death, can occur, these are uncommon complications. HCC is well suited for such injections also because these tumors are most often soft and lie in a hard, cirrhotic liver. The injected alcohol tends to diffuse well within the soft tumors for good coverage of the cancerous tissues.

Because of technical limitations, only tumors smaller than 3 cm are generally treatable by PEI.[173] In addition, most clinicians are unwilling to treat more than three tumors by this method. Tumors at the dome of the liver are difficult to treat because of overlying lung and the risk of pneumothorax. Patients with ascites are poor candidates for such injections, as the risk of bleeding is higher in these patients because the abdominal wall is not directly against the liver and cannot act to tamponade the sites of injection.

When tumors are within the limits for injection, results are very good. Nonrandomized studies have demonstrated a 3-year survival rate of 55% to 77% after PEI.[172,174–176] In one large phase II trial that included 210 patients, the 5-year survival was found to be 33%.[177] These treatments are unlikely to be curative, however. Patients should be followed up closely by imaging, and repeated treatments should be given when appropriate.

In a nonrandomized case study comparing liver resection (n = 33) with PEI (n = 30) in the treatment of small (<4-cm) HCCs, the recurrence rate was higher with PEI, but 1- and 4-year survival rates were similar for both treatment modalities.[175] Two randomized, controlled trials have been performed, one comparing PEI to no treatment[178] and the other comparing PEI plus transarterial chemotherapy to transarterial chemotherapy alone.[179] No definitive differences were found, but this may be due to small sample size.[146]

Currently, we use PEI as the ablative method of choice for small (<3 cm) HCCs of limited number (<3) in Pugh-Child's grade A or B cirrhotics in whom resection is not possible. The procedure is well tolerated and the risks minimal. Patients are followed up closely, and treatments are repeated when viable tumor is again demonstrated. Larger trials comparing this technique with supportive care and other ablative techniques are sorely needed for patients with unresectable small tumors. In addition, for patients with resectable small tumors, a comparative study of resection versus PEI is important. The greatest limitation to PEI, however, is that few patients in the Western world present with tumors of sufficiently small size for such treatments.

Tumor ablation can also be accomplished by injection of other agents. Agents so tested have included acetic acid, hot saline, glass microspheres containing ^{90}Y, and various chemotherapeutic drugs.[180] Partial and complete destruction of tumors has been documented with each of these. However, an advantage of any of these agents over ethanol has not been demonstrated to date. Ethanol is so well tolerated and the procedure so simple, particularly as compared to injections of radioactive isotopes, that until results from future comparative trials demonstrate a better alternative, PEI remains the treatment of choice for small, locally limited HCC.

CRYOSURGERY. Repeated freezing and thawing of tissues also produces tissue destruction. Recent technologic advancements have allowed for design and mass marketing of vacuum-sealed probes that are cooled by liquid nitrogen or argon. These probes can be introduced into tumors, and freezing can be performed under ultrasound guidance until the ice ball is more than 2 cm beyond the tumor margin. The tumor then is thawed and frozen again to produce effective cryoablation. The major advantage of this method over ethanol injection is the relatively larger size of tumor that can be treated effectively by cryoablation. Using probes of a diameter of 2 to 3 mm, a 5- to 6-cm ice ball can be produced. By placing multiple probes in proximity to one another, ice balls of up to 10 cm can be produced.

The major disadvantage is the need for general anesthesia and laparoscopy or laparotomy. Furthermore, not only is freezing of tumors near major vascular channels difficult because of the risks of bleeding, but complete freezing is virtually impossible because warm blood circulates in the vessels.

A number of series have been published that clearly demonstrate the safety of such an ablative approach in experienced hands.[181,182] Recently, as smaller and smaller cryoprobes have become available, some investigators have also attempted to perform the cryoablation percutaneously. Whether this will represent an advance is not yet known. Certainly, comparative studies of cryoablation to nonsurgical ablative methods such as ethanol injection or embolization are needed.[174,183,184]

In our practice, we are prepared to perform cryoablation whenever an operation is performed to attempt resection. If a tumor is found to be unresectable at the time of surgery, and the patient has already incurred the risks of anesthesia and laparotomy, we will proceed with cryoablation if it is technically feasible. We will also perform cryoablation for patients with clearly unresectable cancers in whom nonsurgical forms of ablative therapy fail.

RADIOFREQUENCY ABLATION. An ablation technique that is becoming increasingly popular is radiofrequency ablation (RFA). In this ablative modality, heat as generated by a radiofrequency electrode is used to kill tumors. The radiofrequency electrode is passed under radiologic guidance into the tumor of interest and tumor is ablated by thermal energy. The major advantage of RFA results from the small diameter of the electrodes, which allows routine percutaneous and laparoscopic ablation.[185–187] RFA equipment is also much less expensive than is cryotherapy equipment and is more portable and easier to maintain. However, RFA is limited by the small size of tumors that can be completely ablated by current radiofrequency instruments. As heat is generated within the tumor, charring of tissues occurs, decreasing the conduction of heat. The result is that tumors of only 3-cm diameter or smaller can currently be ablated reliably. In addition, in contrast to cryoablation, wherein the ice ball appears unequivocally as a homogeneous, hypoechoic lesion on US, the RFA lesion is much more difficult to follow radiographically.

The published experience to date on use of RFA is meager.[186,188] It is already clear, however, that patients tolerate RFA well. The tumors treatable by RFA are currently being treated by PEI. RFA carries a theoretically lower risk of bleeding, as the needle track can be coagulated during withdrawal of the radiofrequency electrode. PEI however, is simpler, less expensive, and has a longer track record. A direct trial comparing these two techniques is essential. For now, PEI represents the standard ablative modality for unresectable, small HCC, though RFA is a promising investigational treatment for this same population.

HEPATIC ARTERIAL EMBOLIZATION. The liver has a dual nutrient blood supply consisting of the hepatic artery and the portal vein. Under normal conditions, the hepatic parenchyma derives most of its nutrients from the portal vein, and complete occlusion of the hepatic artery does not render the liver ischemic. In contrast, hepatic tumors derive most of their nutrients from the hepatic artery. To induce ischemia and death of unresectable tumors, surgical hepatic arterial ligation was at one time the treatment of choice but has largely been abandoned for two main reasons. First, long-term clinical efficacy is poor, probably owing to the rapid development of collateral vessels after ligation of the main vessels.[189] Second, in patients with cirrhosis and portal hypertension, a high percentage of nutrient blood supplying functional noncancerous parenchyma is derived from the hepatic artery. Ligation of the main hepatic artery therefore was associated with a high procedure-related mortality, as high as 13%. Hence, this procedure has largely been abandoned as a treatment mode for HCC in the cirrhotic patient.[118,190]

Percutaneous selective TAE is a much safer method for treating liver tumors when vascular interruption is desired and has largely replaced surgical arterial ligation. In this method, a catheter is introduced through a percutaneous femoral approach and is threaded under fluoroscopic guidance to the hepatic artery. The branch feeding each tumor can then be cannulated selectively and occluded with degradable or nondegradable particles, coils, or oils. Such selective embolization maintains patency of the main hepatic arteries, thus sparing normal functional liver parenchyma. In addition, it allows repeated treatments through the same arteries. Possible adverse effects include pain, fever, nausea, and transient increase in liver enzymes.[191] Hepatic insufficiency and infected necrotic tumor are rare complications but may be a cause of treatment-related mortality. The risk of complications is clearly related to the degree of hepatic dysfunction. Treatment-related mortality is as high as 80% in patients with Pugh-Child's grade C hepatic function.[71] Therefore, embolization generally is performed only for patients with Pugh-Child's grade A or B liver function. In addition, patients with portal vein occlusion tolerate arterial interruption very poorly, and presence of tumor thrombus in the main portal vein is considered a relative contraindication to embolization.

There is no doubt that such embolization produces objective responses in approximately one-half the patients (Table 33.5-10).[192–196] For patients with painful, unresectable tumors, embolization is effective therapy. It can also be life-saving therapy for patients with ruptured HCC.[197] Documenting the benefits of embolization in other settings has been more difficult. Randomized studies comparing TAE to chemotherapy[198] or to supportive care[199–201] have been unable to document an improvement in survival. However, most studies are plagued by difficulties and

TABLE 33.5-10. Embolization and Chemoembolization for Hepatocellular Carcinoma

Study	*No. of Cases*	*Survival*			*Embolic Agent*	*Chemotherapy*	*Response (%)*
		1-Y	2-Y	3-Y			
Kanematsu et al., 1989[193]	149	56	29	17	O	D	47
Nakamura, 1989[564]	100	52.8	33.3	17.6	G, O	D	—
	104	45.2	16.3	3.8	G	D, M	—
Shibata et al., 1989[564a]	71	55	—	—	O	C	47
Pelletier et al., 1990[565]	42	24	—	—	G	D	17
Venook et al., 1990[566]	50	—	—	—	G	D, M, C	24
Yamada, 1990[567]	793	51	24	NR	G	D, M	—
Nakao, 1991[568]	66	88	57	42	G, O	D, M	—
Bismuth, 1992[72]	291	62	26	NR	G, O	D	—
Rougier et al., 1993[595]	232	—	—	—	G, O	D	41
Stuart et al., 1993[569]	52	—	—	—	G, O	D	43
Uchida, 1993[570]	863	60.7	37.7	22.4	G, O	D	—
	57	93.2	71.6	49	O	D	—
	212	48.6	24.9	12.7	G	None	—
Carr et al., 1994[195]	56	—	—	—	O	D, C	57
Carr et al., 1995[571]	26	—	—	—	G	D, C	58
Chung, 1995[572]	110	30	18	9	G, O	D, M	31
Ryder et al. 1996[206]	67	—	—	—	O	D	22
Ngan et al., 1996[196]	132	55	33	25	G, O	C	56
Brown, 1997[192]	46	50	32	~29	PVA	None	—

C, cisplatin; D, doxorubicin; G, Gelfoam; M, mitomycin; O, oils (Lipiodol-Ethiodol); PVA, polyvinyl alcohol.

flaws, including small sample size. More important, treatment in these studies has usually involved embolization of the main hepatic arteries rather than the safer and more effective selective embolization performed at major centers.

To improve on the efficacy of embolization, investigators have attempted to soak the embolization particles, such as Gelfoam, with chemotherapeutic agents prior to delivery by chemoembolization. In two randomized studies of chemoembolization versus embolization alone, however, there were no differences in survival.[202,203]

In other attempts to improve the results of TAE, investigators have used Lipiodol or ethiodized oil (Ethiodol). Each of these agents is a lymphangiogram dye derived from poppy seed oil that selectively wedges within HCC when administered via the hepatic artery.[204,205] Embolization of tumors using these oils was originally developed to enhance visualization of HCC. It then was discovered that these oils can be used to deliver and concentrate chemotherapeutic agents at sites of tumor. By mixing hydrophilic drugs with Lipiodol, an emulsion is produced that can be administered intraarterially to produce Lipiodol chemoembolization.

Phase I and II studies and small phase III studies have demonstrated a significant tumor response rate after such treatment. Treatment with doxorubicin and Lipiodol produced responses in 10 of 18 patients with small HCCs (<4 cm) and in 5 of 49 patients with large tumors.[206] Yoshikawa et al.[207] randomized 19 patients to receive Lipiodol-epirubicin and compared them with 17 patients who received epirubicin alone through the hepatic artery. Lipiodol-epirubicin gave a higher tumor response rate as compared with epirubicin alone (42% vs. 12%, respectively).

Larger, randomized trials have been unable to substantiate a survival benefit for such Lipiodol chemoembolizations, however. Madden et al.[208] randomized 136 HCC patients to receive intraarterial Lipiodol-epirubicin versus supportive care and found no survival benefit. Instead, there was an increased morbidity for the treatment arm. A randomized study comparing treatment using Lipiodol plus Adriamycin to Lipiodol alone showed a trend toward a better response at 1 and 2 years with the combination of Lipiodol and Adriamycin, but the difference was not statistically significant.[202]

A further modification of this same theme involved the intraarterial administration of hydrophilic drugs mixed with Lipiodol in an emulsion, followed by temporary or permanent occlusion of the hepatic artery by embolization using a Gelfoam pellet, Ivalon particles, or starch particles. Okuda et al.[194] treated 52 patients with HCC using HAI 5-FU plus cisplatin followed by particle embolization and Lipiodol injections. They reported a response rate of 71% and a 5-year survival of 46%.[194] In another study comparing particle embolization with epirubicin and Lipiodol versus chemotherapy alone in 38 patients, the 1- and 2-year survivals were 73 and 35 versus 43 and 0 in the two groups, respectively.[207] A randomized study comparing intraarterial Lipiodol-cisplatin and Gelfoam embolization to supportive care showed no improvement in survival among the treated group, though this is likely attributable to the high incidence of liver failure in the treated patients.[200] Another randomized study comparing treatment with Lipiodol-cisplatin plus Gelfoam embolization to Lipiodol and Gelfoam in patients with HCC showed a worse outcome in the group using cisplatin.[203] The case for chemoembolization with or without Lipiodol administration is, therefore, far from proven. Because of the small size of individual studies, metaanalyses of the published randomized studies have been performed[146] but have failed to show any clear benefit of transarterial chemoembolization over no treatment.

Particle embolization clearly produces responses in the majority of tumors. At times, the response can be very dramatic, resulting in impressive relief of symptoms. Hence, these treatments may be useful in a patient with ruptured tumors or tumors that are symptomatic in pain or paraneoplastic syndromes. In addition, it is our bias (though not yet supported by randomized trials) that, for the subset of patients with good liver function, tumors of less than 10 cm in diameter, less than 50% liver replacement by tumors, and no portal vein thrombus, selective embolization may be beneficial. It is in this favorable subset of patients that future clinical trials should be directed, examining the utility of embolization. We believe that current data do not support the use of chemoembolization or Lipiodol mixtures but rather indicate that these complex mixtures may merely add cost and complications without improving efficacy. At present, we prefer to use simple particle embolization for treatment of symptomatic or favorable tumors. It is likely that effective palliative therapy will be a combination of local therapy by embolization and an as-yet unidentified systemic treatment.

Radiotherapy

Initial attempts to use whole liver radiation in the treatment of primary hepatobiliary cancer were unsuccessful.[209,210] For instance, in the series by El-Domeiri et al.[209] and Phillips and Murikami,[210] only 1 of 31 patients with unresectable disease who underwent radiation survived more than 1 year. The most important reason for this lack of success is the low tolerance of the liver to whole organ radiation. Indeed, the radiation tolerance of the whole liver in patients with primary HCC may tend to be lower than in those with metastatic cancer to the liver, as many patients with primary disease have some degree of underlying cirrhosis.

Attempts have been made to increase the effectiveness of whole liver irradiation in the treatment of patients with unresectable hepatoma by the addition of intravenous chemotherapy[211,212] and ^{131}I antiferritin monoclonal antibody therapy.[213,214] Radiation Therapy Oncology Group (RTOG) trial RTOG 85-19 was a randomized trial assessing the benefit of adding ^{131}I antiferritin monoclonal antibody therapy to doxorubicin and 5-FU for patients who had received initial treatment with doxorubicin plus 5-FU and whole liver irradiation (21 Gy in seven fractions).[214] RTOG 88-23 measured the benefit of combining antibody with hepatic artery cisplatin for patients who had received induction treatment with whole liver irradiation (21 Gy in seven fractions) and intravenous cisplatin. The conclusions from these and other studies[215] are that ^{131}I antiferritin increased toxicity without benefit and that hepatic arterial cisplatin may be superior to either intravenous[211] or hepatic arterial[212] doxorubicin and 5-FU when combined with irradiation. The finding that hepatic arterial cisplatin and radiation can produce an objective response rate of 45% and a median survival of 7.5 months in a relatively large group of patients[76] suggests that these combinations have some activity.[215]

In contrast to the relative ineffectiveness of whole liver irradiation (when used alone), focal liver irradiation can produce regression of primary hepatobiliary cancers (Fig. 33.5-3). At

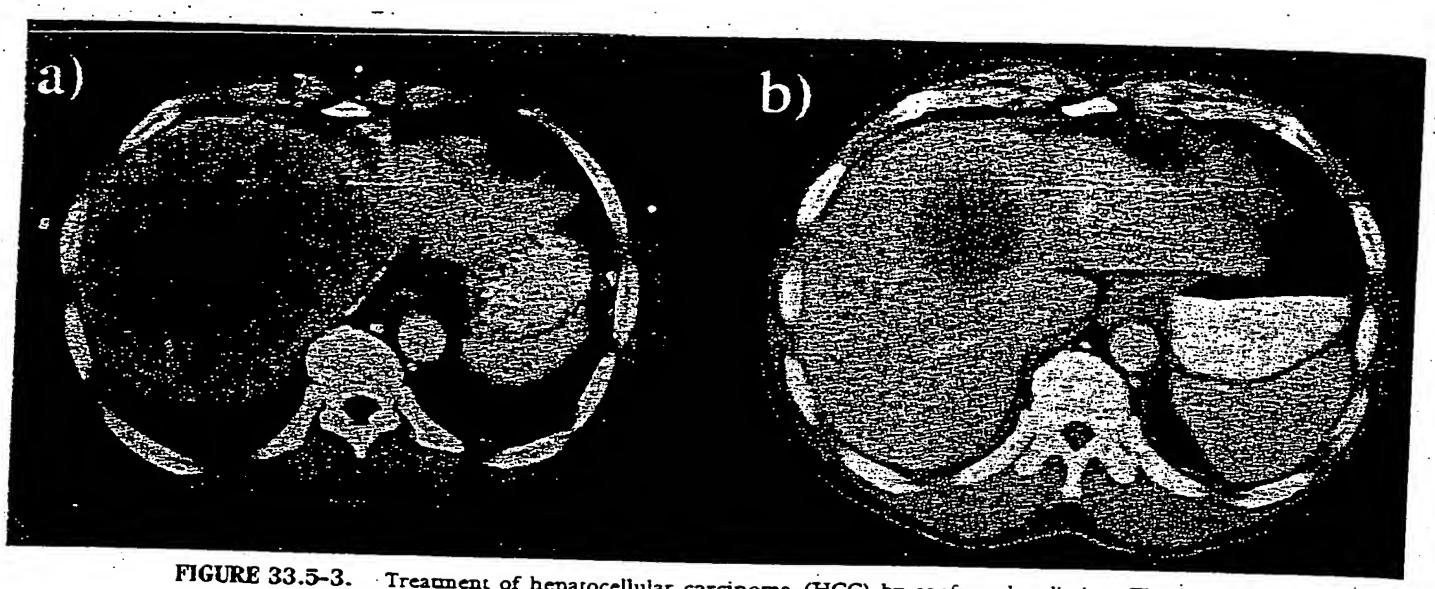

FIGURE 33.5-3. Treatment of hepatocellular carcinoma (HCC) by conformal radiation. The large HCC in the right lobe of the liver (A) has had a dramatic response (B) to such treatment.

least four techniques have been assessed: ^{90}Y microspheres, ^{131}I-labeled ethiodized oil, and external-beam radiotherapy with either protons or photons. In ^{90}Y therapy, ^{89}Y oxide is incorporated into a stable glass matrix. When bombarded with neutrons, ^{89}Y is converted to ^{90}Y, a pure beta emitter with a half-life of 64.5 hours and average electron energy of 2.23 MeV, which produces an electron range of approximately 2.5 cm. The microspheres have been infused into the hepatic artery as a form of regional therapy for well-vascularized tumors, producing objective response rates ranging from 0% to 25%[109,216–218] (for review, see Ho et al.[219]). Note that ^{90}Y doses (50 to 150 Gy) cannot be compared directly to the more familiar external-beam doses, as the former are calculated by assuming full decay with all radiation homogeneously deposited within the liver. More important, low dose-rate irradiation (<0.2 Gy/h) delivered by ^{90}Y has far less effect than the same physical dose delivered by standard external-beam treatment (>2 Gy/min). A better understanding of the dosimetry of this technique[220] as well as of the technical factors (such as pulmonary shunting, which can lead to radiation pneumonitis,[221] or variant arterial supply to the stomach, which can produce gastric ulcers) is required before the application of microspheres can become routine. ^{90}Y microspheres are not available for clinical use in the United States currently.

Another method of delivering focal liver irradiation involves hepatic arterial administration of ^{131}I ethiodized oil. Ethiodized oil has been used extensively for chemoembolization for HCC (discussed earlier in the section Hepatic Arterial Embolization); in this approach it is formulated with radioactive iodine in an attempt to deliver localized irradiation using the beta (electron) component of the ^{131}I emissions.[222,223] Randomized trials led by French investigators compared ^{131}I-labeled ethiodized oil to chemoembolization[224] and ^{131}I-labeled ethiodized oil to supportive care for patients with portal vein thrombosis.[225] In the former study, 129 patients were randomized to receive either 60 mCi of ^{131}I-labeled ethiodized oil or chemoembolization with cisplatin (70 mg). There was no difference in overall survival between the two groups (median survival, approximately 40 weeks), but the toxicity of the ethiodized oil arm was significantly less. In the latter study, 27 patients were randomized to receive either 60 mCi of ^{131}I-labeled ethiodized oil or control treatment (such as tamoxifen). The ethiodized oil group showed a statistically significantly greater median survival (approximately 6 months as compared to 2 months). Although these findings suggest that ^{131}I-labeled ethiodized oil has activity in HCC, this small study does not permit a firm conclusion to be drawn. Furthermore, as is the case for ^{90}Y, little is known about the tumor and normal tissue dosimetry. ^{131}I-labeled ethiodized oil is not available for use in the United States.

Traditional external-beam photon techniques, either alone[226] or in combination with chemoembolization,[227] have produced objective responses in patients with unresectable HCC. However, standard photon techniques often require the treatment of large volumes of normal liver. In contrast, three-dimensional conformal radiotherapy (3D-CRT) planning using beams not confined to the axial plane can substantially reduce irradiation of normal liver.[228,229] Phase I and II trials for patients using 3D conformal external-beam irradiation combined with hepatic arterial FUDR have demonstrated that high-dose focal irradiation can produce a 60% response rate (see Fig. 33.5-5).[230,231] Recent results support the hypothesis that the dose delivered is an important prognostic factor in both local control and survival for patients with primary hepatobiliary cancers. In this study, dose is prescribed (to a maximum of 90 Gy) according to the fraction of normal liver that is spared, based on a normal tissue complication probability (NTCP) model. Patients who can receive more than 70 Gy have a median survival in excess of 17 months, which approaches that achieved by surgical resection. In a multivariate analysis, dose is a prognostic factor independent of tumor size.[232]

Although 3D techniques permit parts of the liver to be treated with doses of radiation far higher than the entire liver can tolerate, it is possible that both higher doses and larger volumes than have been used in the current studies could be used safely. A first step in defining these limits is to develop an NTCP model to describe the dependence of liver tolerance on the combination of dose and volume. A number of theoretic

models (all of which require knowledge of the 3D dose distribution) have been proposed to estimate the volume dependence of normal tissue tolerance.[233-235] Initial investigations have suggested that it will be possible to derive a quantitative model to predict radiation-induced liver disease.[235] More recently, an NTCP model with parameters calculated from patient data has been used prospectively to prescribe a dose that would subject each patient to a predetermined complication risk. Twenty-one patients have completed treatment on such a protocol. The mean dose delivered was 56.6 ± 2.3 Gy (range: 40.5 to 81 Gy). One of 21 patients developed radiation-induced liver disease. The observed complication rate of 4.8% (95% confidence interval, 0% to 23.8%) did not differ significantly from the predicted 8.8% NTCP (based on dose delivered). These results suggest that an NTCP model can be used prospectively to deliver safely far higher doses of radiation to patients with intrahepatic cancer than were possible using previous approaches.[236] The widespread adoption of 3D conformal planning systems should permit these concepts to be tested in multiinstitutional trials.

Another method of delivering highly conformal radiation is with protons. Investigators at the Proton Medical Research Center in Japan have demonstrated response rates similar to those just reported using 3D-CRT.[237,238] Interestingly, high-dose focal irradiation using either photons[239] or protons[240] can produce hypertrophy in the nonirradiated liver, resembling the effect of partial hepatectomy.

In summary, whole liver irradiation alone has little efficacy in the treatment of HCC. The addition of hepatic arterial cisplatin may increase the efficacy somewhat. High-dose focal irradiation, especially using external-beam photons or protons, can produce objective responses in the majority of patients, although the relative merit of these techniques as compared to other nonsurgical approaches described in this chapter has not been assessed in randomized trials.

SCREENING FOR HEPATOCELLULAR CARCINOMA

Patients found to have small (<5-cm) HCC have a much better prognosis than do those presenting with larger tumors. The size of a tumor is a significant risk factor for intrahepatic and extrahepatic spread.[241-243] The frequency of intrahepatic metastases rose by almost one-third between HCCs smaller and larger than 5 cm (60% to 90%), and the rate of portal vein tumor thrombosis almost doubled (40% to 75%).[242,243] Many more treatment options are also available for patients with small tumors. Tumors smaller than 3 cm can be treated by PEI, RFA, resection, or transplantation, whereas tumors smaller than 5 cm can be treated by cryoablation, resection, or transplantation. Hence, smaller tumors are not only biologically more favorable but are technically more easily treated. Because symptomatic tumors are usually large, widely disseminated, and beyond therapeutic option, the rationale for screening patients at risk for HCC is clear.

Whole population screening, even in areas where HBV is endemic, is almost certainly not a financially viable option. In epidemiologic studies, it is apparent that the incidence of HCC in HB_sAg-positive patients is approximately 0.5% annually.[244] Therefore, the yield for screening programs is low. Hepatitis occurs mainly in developing countries, where the cost of any population screening program will also be too prohibitive.

In the presence of HCV, however, the risk of HCC in a patient with established cirrhosis is estimated to be as high as 5% per year.[15] Also, HCV occurs more often in industrialized nations. Hence, it is much more justifiable and likely that screening programs will be developed for detection of HCC in patients with cirrhosis due to HCV infection.

As a clinician striving to deliver optimal care for individual patients, screening high-risk patients for HCC is justifiable. Patients with established cirrhosis or chronic HCV infection are clearly important candidates for screening. Patients with chronic HBV infection should also be considered for screening. Furthermore, only patients with Pugh-Child's grade A or B liver functional status should be screened, as patients with Pugh-Child's grade C disease will generally be too sick for therapeutic interventions and early detection of HCC will only cause anxiety and detrimentally affect the patient's likelihood for liver transplantation. Screening protocols are largely based on the biases of each major center. Some have advocated frequent testing, including ultrasound examination every 3 months[245] and serum AFP testing once every 2 months.[246] Because HCC is slow-growing, however, with a documented median doubling time of 4 to 5 months for small HCCs,[245] we advocate AFP and liver function tests every 3 months and liver imaging every 6 months.

OTHER PRIMARY TUMORS OF THE LIVER

HEPATOBLASTOMA

Hepatoblastoma affects approximately 1 in 100,000 children and is the most common primary malignant liver tumor in children.[247,248] It is usually diagnosed before the age of 3 years, with a 2:1 male predominance. Patients usually present with abdominal swelling[247,248] and elevated serum AFP (>75% of patients).[249] CT scans will reveal a vascular mass that often (50%) is speckled with calcifications.[249] The Children's Cancer Study Group staging system is shown in Table 33.5-11.[250] Overall long-term survival varies between 15% and 37%.[249,251-253] Poor prognosis is associated with unresectable tumors and tumors demonstrating aneuploidy and anaplastic characteristics.[251,254,255]

Complete resection is possible in 50% to 65% of children with hepatoblastoma and is associated with cure rates between 30% and 70%.[247,248] Unlike adult primary liver tumors, chemotherapy may produce response in a significant number of patients with hepatoblastomas. Preoperative chemotherapy has been used with some success in converting unresectable tumors to resectable

TABLE 33.5-11. Children's Cancer Study Group Staging for Hepatoblastoma

Group I	Complete resection of tumor by wedge, lobectomy, or extended lobectomy as initial treatment
Group IIA	Tumor rendered completely resectable by initial irradiation and chemotherapy
Group IIB	Residual tumor confined to one lobe
Group IIIA	Tumor involving both lobes of the liver
Group IIIB	Regional lymph node involvement with tumor
Group IV	Distant metastases of tumor regardless of the extent of liver involvement

lesions.[256,257] Adjuvant chemotherapy has also been used after resection of hepatoblastoma.[250] Evans et al.[250] reported that 20% of 24 patients with hepatoblastoma were relapse-free 8 to 42 months after surgical resection coupled with adjuvant vincristine, doxorubicin, 5-FU, and cyclophosphamide.

Radiotherapy has been used in the treatment of unresectable hepatoblastomas, but its utility is far from proven.[256,258] Orthotopic liver transplantation should be considered in children with unresectable hepatoblastoma if the tumor does not become resectable after preoperative chemotherapy. Penn[259] reported on 18 patients undergoing liver transplantation for unresectable hepatoblastoma. Though tumors recurred in six patients, five have survived disease-free for more than 2 years, with actuarial survival rates of approximately 50%.

ANGIOSARCOMA

Angiosarcomas are malignant mesenchymal tumors of the liver that are also referred to as *hemangiosarcomas*. Only approximately 25 cases occur in the United States each year.[260] Peak incidence is in the sixth and seventh decades, with a predominance in men (85%).[261] Abdominal pain, abdominal swelling (usually due to liver enlargement), liver failure, nausea, anorexia, vomiting, and jaundice are seen. These malignant tumors have been associated with exposure to thorotrast, arsenic, or vinyl chloride.

Angiosarcomas are aggressive neoplasms. Partial hepatectomy can result in long-term survival, but most patients present with advanced tumors that cannot be treated by excision. Distant metastases are found at initial presentation in one-half of patients. Most patients die within 6 months of diagnosis. Even with surgical excision, few patients survive more than 1 to 3 years after complete resection because of metastatic disease. Results of radiotherapy and chemotherapy or both have been disappointing.[261] The results of orthotopic liver transplantation for treatment of angiosarcoma have also been poor. Penn et al. reported development of tumor recurrences in 9 of 14 transplant patients with tumors classified as either angiosarcomas or epithelioid tissue sarcomas. The 2-year survival rate was 15%, and no patient survived more than 28 months postoperatively.[259]

The liver can occasionally be the primary site for rhabdomyosarcoma,[262] though this is more common in children than in adults. Hepatic metastases from a gastrointestinal or uterine primary tumor must be ruled out before the diagnosis of primary leiomyosarcoma of the liver can be made. Surgical resection is the treatment of choice for these primary hepatic sarcomas.[262] Unresectable disease carries an unfavorable prognosis.

Undifferentiated sarcomas of the liver are very rare and usually occur in children between the ages of 6 and 15 years.[263,264] Average age at presentation is 50 years, and the usual presenting signs and symptoms consist generally of nonspecific complaints, including pain, and an abdominal mass. In contrast to angiosarcoma, there is a female predominance (63% of patients).[262] Epithelioid hemangioendothelioma has also been related to vinyl chloride exposure in some patients.[265]

Weiss and Enzinger[260] recommended radical surgery, if possible. However, these tumors are almost always diffuse and multifocal and, therefore, are unlikely to be cured by partial hepatectomy. If hemangioendothelioma is suspected, a percutaneous biopsy is performed for diagnosis. Frozen-section analysis is not usually helpful at open surgery because special stains are required for diagnosis of this tumor. Patients with hemangioendotheliomas should be considered for total hepatectomy and liver transplantation. Penn[259] reported a series of 21 patients who underwent orthotopic liver transplantation for treatment of epithelioid hemangioendotheliomas; 7 of 21 patients experienced tumor recurrence. The actuarial survival rate was 82% at 2 years and 43% at 5 years.

CHOLANGIOCARCINOMA

Cancers of the bile ducts are rare tumors, with only approximately 4000 cases presenting in the United States annually. Because of the proximity of the bile duct to the liver, the pancreas, and major vascular structures, surgical excision of these tumors usually requires a major hepatic or pancreatic resection or both. Major vascular reconstructions may also be necessary. The technical demands of such resections and the lack of effective alternative therapies for cholangiocarcinomas explain the nihilistic attitude that generally surrounds this disease. Advances in imaging over the last two decades now allow for earlier diagnosis of bile duct cancer and better surgical planning. Recent improvements in operative technique have substantially improved the outlook of patients presenting with this cancer.

EPIDEMIOLOGY AND ETIOLOGY

Cholangiocarcinoma is an uncommon cancer, with an incidence of 1 to 2 cases per 100,000 population in the United States[266] and constituting approximately 2% of all reported cancers.[267] It is a disease of the elderly, with the majority of such lesions occurring in patients older than 65 years and the peak incidence occurring in the eighth decade of life.[266] Untreated, bile duct cancers are rapidly fatal diseases, and the majority of patients will die within 6 months to a year of diag-

Primary Sclerosing Cholangitis

In Western nations, the disease most often associated with development of cholangiocarcinoma is primary sclerosing cholangitis (PSC). This is an autoimmune disease characterized by inflammation of the periductal tissues and, at advanced stages, is characterized by multifocal strictures of the intrahepatic and extrahepatic bile ducts.[272–274] The majority (70% to 80%) of patients with PSC also have associated inflammatory bowel disease in the form of ulcerative colitis.[272] In a longitudinal study of patients with PSC, 8% of patients developed clinically apparent cholangiocarcinoma over a 5-year period.[272] This explains the high incidence (30% to 40%) of occult cholangiocarcinoma found in autopsy or explant specimens from patients with PSC.[272–274] Cholangiocarcinomas presenting in patients with PSC are often multifocal and not amenable to treatment by partial hepatectomy. Liver transplantation is often the only treatment possible for these patients, not only because of multifocal cancer but also because of the baseline hepatic insufficiency from the underlying inflammatory disease.

Choledochal Cysts or Caroli's Disease

The increased risk of cholangiocarcinoma in patients with congenital cystic disease of the biliary tree is well recognized.[275,276] The reason for the malignant transformation is thought to be related to chronic inflammation and bacterial contamination within the cystic areas.[276–279] Early excision of the choledochal cyst significantly reduces the risk of cancer.[276,277] Fifteen to twenty percent of adult patients with unexcised choledochal cysts or cysts previously treated with bypass will be found to have a cholangiocarcinoma.[276,277]

Pyogenic Cholangiohepatitis and Other Hepatic Infections

In the Orient, chronic infections of the liver can predispose to development of cholangiocarcinoma. Pyogenic cholangiohepatitis or Oriental cholangiohepatitis results from chronic portal bacteremia and portal phlebitis, which gives rise to intrahepatic pigment stone formation. This hepatolithiasis leads to recurrent episodes of cholangitis and stricture formation.[280–283] Those patients who do not succumb to sepsis will have approximately a 10% chance of developing cholangiocarcinoma.[281–283] In Southeast Asia, biliary parasites (*Clonorchis sinensis, Opisthorchis viverrini*) are also associated with an increased risk of cholangiocarcinoma.[273] In areas where these parasites are endemic, the incidence of cholangiocarcinoma is as high as 87 per 100,000.[284]

Influence of Environmental Agents

Several radionuclides and chemical carcinogens, including thorium, radon, nitrosamines, dioxin, and asbestos, have also been implicated in the development of cholangiocarcinomas.

PATHOLOGY AND CLASSIFICATION

Cholangiocarcinoma can arise anywhere within the biliary tree. Approximately 10% of cholangiocarcinoma cases arise within the intrahepatic bile ducts.[285–289] These usually present as hepatic masses that are thought at first to be HCCs or metastatic tumor of unknown origin. The extrahepatic variety is more common and can occur along the entire length of the bile duct from the confluence of the hepatic ducts to the ampulla. Some have classified these extrahepatic tumors into proximal (hilar), middle, and distal bile duct tumors. Nakeeb et al.[290] proposed a more practical division of cholangiocarcinomas into intrahepatic, perihilar, and distal subgroups, thus eliminating the midduct group. Those lesions that are proximal to the cystic duct–common duct junction usually require a liver resection for extirpation. These represent approximately 40% to 60% of cases of cholangiocarcinoma and include the hilar cholangiocarcinomas or Klatskin tumors.[270,290–296] Those tumors distal to the cystic duct usually require pancreatectomy for treatment. Fewer than 10% of patients will present with multifocal or diffuse involvement of the biliary tree.[297]

Cholangiocarcinomas are characterized by early invasion of adjacent organs.[298] Nodal metastases are also common and occur in up to one-third of cases.[270,299] In addition to lymphatic involvement, these tumors are also characterized by neural, perineural, and subepithelial extension.[298]

Cholangiocarcinomas can be separated into three distinct macroscopic subtypes: sclerosing, nodular, and papillary.[298] Most are *sclerosing* tumors, which are very firm and are seen as annular thickening of the bile duct, often with diffuse infiltration and fibrosis of the periductal tissues. *Nodular* tumors are firm tumors that project into the lumen of the duct. Frequently, features of both sclerosing and nodular tumors are found, and the tumor is described as *nodular-sclerosing*. *Papillary* tumors are soft and friable and often demonstrate little transmural invasion. These tumors have a more favorable prognosis than do the others,[273] are more common in the distal bile duct, and account for approximately 10% of all cholangiocarcinomas.[298]

The overwhelming majority (>90%) of cholangiocarcinomas are adenocarcinomas, often well differentiated and mucin-producing.[266,298,300] Rarely, malignant obstruction of the bile duct may be due to other cell types, such as carcinoid tumors, arising primarily in the biliary tree or to tumors metastatic to the biliary tree.[301–303]

DISTAL BILE DUCT CANCERS

Distal bile duct cancers are rare cancers that usually are reported as part of a series of periampullary tumors or as a series describing all bile duct cancers. Distal bile duct tumors represent approximately 20% to 30% of all cholangiocarcinomas or 5% to 10% of all periampullary tumors.[290,293,294,304] Approximately 2000 new cases of distal bile duct cancer are diagnosed in the United States each year.[293] They are almost always adenocarcinomas. The papillary variety is also more common in this location than in other parts of the bile duct.[292]

Clinical Presentation and Diagnosis

On the practical level, patients with distal bile duct cancers usually present with jaundice and a mass at the head of the pancreas. Except in the case of the papillary variety of this cancer, patients are brought to the operating room with the diagnosis of periampullary cancer, and it is in the final pathologic analysis that the anatomic site of origin of the tumor becomes clear. The importance of distinguishing distal bile duct cancer from the other periampullary tumors is in the prognostic implications, as

distal bile duct cancer has a much more favorable outcome than does the more common adenocarcinoma of the pancreas.

Jaundice is the presenting symptom in up to 90% of patients with distal bile duct cancer. Abdominal pain, weight loss, fever, or pruritus are also common symptoms, though these occur in one-third of cases or fewer.[290,295] If the patient reports that the jaundice is intermittent, a papillary bile duct cancer should be suspected. Most often, however, the symptoms and signs will be indistinguishable from adenocarcinoma of the pancreatic head or other periampullary malignancies.

US will demonstrate a dilated extrahepatic and intrahepatic biliary tree. Cross-sectional imaging by CT scanning will usually then demonstrate a mass in the region of the head of the pancreas. Endoscopic retrograde cholangiopancreatography (ERCP) may be diagnostic if it demonstrates an obstruction in the bile duct that does not involve the pancreatic duct. Most often, however, ERCP will demonstrate distal biliary obstruction without diagnostic information on the cell origin of the malignancy. In fact, we tend not to perform ERCP if the patient is a surgical candidate, preferring to operate on the patient without direct biliary manipulation, as this decreases the risk of biliary sepsis.[305]

If surgical resection is planned, a preoperative tissue diagnosis of cancer is not necessary and often is not possible. Endoscopic brush biopsy has a low sensitivity, making a negative result virtually useless.[306] Performing a percutaneous needle biopsy is difficult because of the small size of these tumors. Therefore, preoperative diagnosis is usually based on clinical impression. In patients with a stricture of the distal bile duct and a clinical presentation consistent with cholangiocarcinoma, cross-sectional imaging studies are scrutinized for signs of unresectable cancer. In this regard, a contrast-enhanced helical CT scan with overlapping 5-mm sections through the area of the pancreas is the most useful. This test allows for evaluation for vascular involvement or metastatic disease. Magnetic resonance cholangiopancreatography (MRCP) may also be used for evaluation of these periampullary tumors.[307]

If the tumor is judged unresectable by radiologic criteria, it is usually of sufficient size for diagnosis by percutaneous needle biopsy. Biliary obstruction then can also be treated by endoscopic stenting or, if necessary, through percutaneous transhepatic stenting to avoid surgery.

Treatment Options

Complete resection is the only effective and potentially curative therapy for cancers of the lower bile duct.[271,290,292–294,304] Resection usually requires a pancreaticoduodenectomy.[293,304] In comparison to pancreatic cancer, distal bile duct cancer is more often amenable to resection and patients less often have microscopic disease at the resection margin and less frequently demonstrate spread of tumor to adjacent lymph nodes.[290,293,294] Completeness of resection, presence of lymphatic metastases,[293,304] and tumor differentiation[290] are the prognostic factors that most strongly influence long-term outcome. Fong et al.[293] found that lymph node status was the only independent predictor of long-term survival in patients who have undergone resection, with positive nodes conferring a 6.7 times greater likelihood of recurrence and death.

The results of resection for distal bile duct cancer as compared to the other periampullary tumors are demonstrated in Figure 33.5-4. The results are similar to those for duodenal cancer, more favorable than those for adenocarcinoma of the pancreas,[293,304] and less favorable than those for neuroendocrine or ampullary tumors. Five-year survival rates of up to 40% have been reported after complete resection (Table 33.5-12). It has long been assumed that survival after resection of distal bile duct tumors is more favorable than after resection of hilar cholangiocarcinomas,[292] but this commonly held belief has been refuted by data. Though it is true that resectability rates are higher for distal bile duct cancers and the likelihood of achieving a negative margin during resection is greater, the survival rates of the various bile duct tumors, if adjusted for stage and completeness of resection, appear to be comparable.[271]

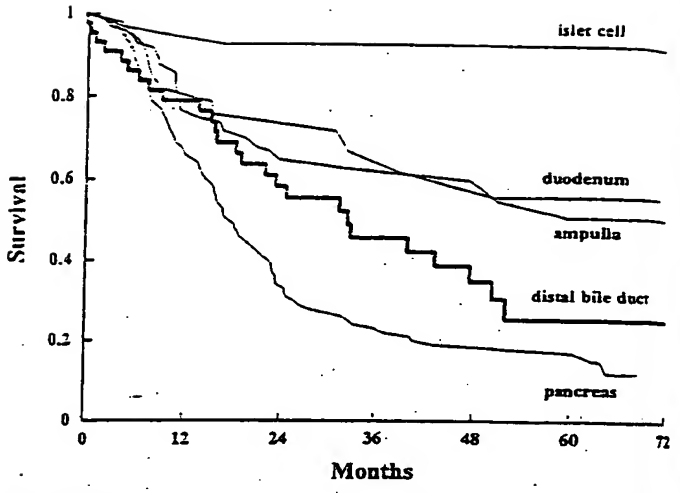

FIGURE 33.5-4. Survival for patients with various peripancreatic tumors.

Because of the rarity of distal cholangiocarcinoma, no prospective data are available to guide the use of adjuvant therapy after resection.[290] We tend not to use adjuvant therapy if resection margins are clear of tumor, though many other practitioners use regimens of chemoradiation originally developed for adenocarcinoma of the pancreas.

In patients with nonresectable cancers, palliation for biliary obstruction can be achieved with a surgical bypass or biliary endoprostheses. Endoprostheses for distal biliary obstruction are usually placed endoscopically and provide more durable palliation than does an endoprosthesis placed for hilar obstruction.[277] Surgical bypasses also provide excellent relief of jaundice and can be achieved with an acceptably low morbidity and mortality. In our practice, patients found to have unresectable disease at laparotomy are subjected to surgical bypasses, as they will already have incurred the risk of anesthesia and laparotomy. Furthermore, patients expected to survive longer than 6 months are also considered for surgical bypass.[308] All other patients are treated with biliary endoprostheses.

Chemotherapy or radiotherapy or both have offered generally poor results as palliative treatment for unresectable cases. Survival beyond 1 year is uncommon in patients subjected to palliative therapies.[290,292,293,304]

PROXIMAL OR HILAR CHOLANGIOCARCINOMA

Proximal or hilar cholangiocarcinomas were first described by Altemeier[341] in 1957 and subsequently by Klatskin[309] in 1965.

TABLE 33.5-12. Survival after Resection of Distal Cholangiocarcinoma

Study	Years	No. of Institutions	Total No. of Patients	No. Resected	Operative Mortality (%)	Median Survival (mo)	3-Y Survival (%)	5-Y Survival (%)
Warren, 1975[573]	30	1	—	47	21	—	32	25
Nakase, 1975[574]	25	57	309	161	22	17	8	5
Tompkins, 1981[292]	25	1	18	12	8	18	28	28
Alexander, 1983[575]	13	1	14	14	21	16	20	18
Lerut, 1983[576]	15	1	—	5	—	11	0	0
Tarazi, 1986[577]	35	1	—	11	0	—	—	17
Nagorney, 1994[271]	10	1	39	22	—	24	40	40
Fong, 1996[293]	10	1	104	45	4	33	46	27
Wade, 1997[504]	4	159	156	34	—	22[a]	—	14
Yeo, 1997[294]	6	1	—	65	—	20	16	—

[a]Mean survival.

Of the hepatobiliary tumors, these cholangiocarcinomas represent the greatest diagnostic and therapeutic challenge because of the vast number of vital structures that can be involved by even a small hilar cholangiocarcinoma. Proximal or hilar cholangiocarcinomas require the most extensive of liver resections and vascular reconstruction for extirpation.

Clinical Presentation and Diagnosis

CLINICAL FINDINGS. Most patients with cholangiocarcinoma come to medical attention because of jaundice or abnormal liver function tests. Other associated symptoms are nonspecific. Abdominal pain or discomfort, anorexia, weight loss, and pruritus are the most common symptoms but are seen in only approximately one-third of patients. Fever usually is seen only after biliary manipulation.[273,274,283,290,510,511] In some patients, pruritus precedes jaundice by some weeks, and this symptom should prompt an evaluation, especially if associated with abnormal liver function tests. Intermittent jaundice may be seen with papillary tumors and is usually due to intermittent detachment of pieces of friable tumors from the right or left hepatic duct that pass into and occlude the common hepatic duct. The serum bilirubin level is usually greater than 10 mg/dL and averages 18 mg/dL, whereas bilirubin levels of 2 to 4 mg/dL are the norm in patients with obstruction from cholelocholithiasis.[512] Malignancy should be strongly suspected in patients with deep, painless jaundice who present with no fever or other signs of infection.

On physical examination, jaundice is usually obvious. Patients with pruritus may have multiple excoriations of the skin. Proximal biliary obstruction is usually associated with a decompressed and nonpalpable gallbladder. Thus, a palpable gallbladder would suggest a more distal obstruction or gallbladder cancer. Signs of portal hypertension are rare but would be an ominous indication of advanced vascular involvement or the alternative diagnosis of cirrhosis and HCC.

Medical history and family history should be scrutinized for conditions such as PSC or Oriental cholangiohepatitis that may predispose to cholangiocarcinoma. Many tumors express carcinoembryonic antigen (CEA) and the carbohydrate antigen CA 19-9. The diagnostic value of these serum markers is, however, debated.[273] It has been suggested that CEA levels in hepatic bile may help to distinguish between benign and malignant strictures in patients with premalignant conditions.[513] Diagnosis of cholangiocarcinoma is usually made radiologically.

RADIOGRAPHIC EVALUATION. Radiologic imaging is central to the diagnosis and treatment planning for patients with cholangiocarcinomas. The importance of imaging studies results from the difficulties in obtaining a positive tissue diagnosis by biopsy, particularly when the tumors are small and in the potentially curable stages. Relying on the results of percutaneous needle biopsy or biliary brush cytology is dangerous, as the results of these tests are often misleading and one may miss the opportunity to resect an early cancer.[514,515] Therefore, the preoperative and, often, operative diagnoses are based mainly on the history and radiologic appearance of the tumors.

The differential diagnosis must include gallbladder carcinoma, Mirizzi syndrome, idiopathic benign focal stenosis (malignant masquerade), or sclerosing cholangitis. Unless there is a large intraluminal mass in the gallbladder, distinguishing gallbladder carcinoma from hilar cholangiocarcinoma can be difficult. Mirizzi syndrome is caused by a large gallstone impacted in the neck of the gallbladder, resulting in biliary obstruction from periductal inflammation.[516–518] Benign focal strictures (malignant masquerade) can also occur at the hepatic duct confluence but are uncommon.[519–522]

Beyond diagnosis, the radiologic evaluation is aimed at determining resectability, as surgical resection is the most effective and only potentially curative therapy. Imaging may locate occult distant metastases and thereby spare patients from nontherapeutic surgery. In defining the degree of invasion of adjacent organs and vasculature, imaging is also essential for planning the surgical procedure and directing major vascular reconstructions when necessary.

Most patients will present to the surgeon having already been subjected to a sonogram and CT. US is usually the first investigation performed because it is noninvasive, readily available, and provides important diagnostic information regarding the jaundiced patient. Generally, intrahepatic biliary dilatation will be seen without evidence of extrahepatic bile duct abnormality and without evidence of stones. In experienced hands, the tumor will often be clearly defined by US, as will information important for planning of surgery such as delineation of

the biliary extent of disease, vascular involvement, presence of lymph node metastases in the porta hepatis, and presence of noncontiguous liver metastases. US not only may demonstrate the level of biliary ductal obstruction but can also provide information regarding tumor extension within the bile duct and in the periductal tissues.[325–325] In centers specializing in treatment of cholangiocarcinomas, a good Doppler US may indeed provide diagnostic information equivalent to that provided by a combination of angiography and CT and is highly accurate in predicting resectability.[325,326] However, US is more operator-dependent than is most cross-sectional imaging. Therefore, in most circumstances, other cross-sectional imaging is necessary.

Most patients will present to a tertiary care center having already been imaged by CT. CT remains an important study for evaluating patients and is less dependent than US on the skills of the operator. Important information regarding level of biliary obstruction, vascular involvement, and presence of nodal or noncontiguous metastases can be assessed. One of the most important findings to be gleaned from a CT scan, however, is the presence of hepatic lobar atrophy, which is usually indicative of portal venous occlusion.[327]

In years past, most patients also were subjected to direct angiography and cholangiography. Angiography allows for determination of arterial or portal venous vascular encasement. Cholangiography demonstrates the location of the tumor and the biliary extent of disease. Recently, however, MRCP has emerged as a noninvasive substitute for direct cholangiography.[328–331] MRCP not only may identify the tumor and the level of biliary obstruction but also may reveal obstructed and isolated ducts not appreciated at endoscopic or percutaneous study. Magnetic resonance angiography (MRA) or CT angiography has become a substitute for direct angiography. Today, the need to perform invasive tests is moot. When direct cholangiography is needed, percutaneous transhepatic cholangiography (PTC) is preferred over ERCP because it is more likely to provide the details of the intrahepatic biliary tree necessary for surgical planning.

For patients presenting with proximal cholangiocarcinomas, a Doppler US, helical CT, and chest radiograph may suffice as preoperative radiologic evaluation. In patients in whom further delineation of biliary or vascular involvement may be necessary, MRCP and MRA are the next tests of choice. This noninvasive approach prevents biliary instrumentation and bacterbilia and the associated increased perioperative morbidity.[305,332] When necessary, direct cholangiography or angiography is used.

Staging

The most commonly used staging systems are the modified Bismuth-Corlette and the American Joint Committee on Cancer (AJCC) TNM (tumor, node, metastasis) staging system. The former classifies patients based on the extent of biliary duct involvement by tumor,[333] whereas the latter is based largely on pathologic criteria (Table 33.5-13). These staging systems do not distinguish between extensive unilateral disease and bilateral disease because, before surgical resections became commonplace, such distinctions had little value. Thus, a patient with tumor extension into third-order biliary ducts on one side of the liver accompanied by ipsilateral portal vein occlusion will be classified as having very advanced disease, though this patient may now be treatable with potentially curative resection as disease is confined to one side.

TABLE 33.5-13. American Joint Committee on Cancer TNM Staging System for Proximal (Hilar) Cholangiocarcinoma and Cancer of the Extrahepatic Bile Ducts

TUMOR (T)	
Tis	Carcinoma *in situ*
T1	Tumor invades subepithelial connective tissue or fibromuscular layer
T2	Tumor invades perifibromuscular connective tissue
T3	Tumor invades adjacent organs (liver, pancreas, duodenum, gallbladder, colon, stomach)
NODE (N)	
N0	No regional lymph node metastases
N1	Metastasis to lymph nodes within the hepatoduodenal ligament (cystic duct, pericholedochal and/or hilar lymph nodes)
N2	Metastasis to peripancreatic, periduodenal, periportal, celiac, superior mesenteric, and/or posterior pancreaticoduodenal lymph nodes
METASTASIS (M)	
M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1 or N2	M0
Stage IVA	T3	Any N	M0
Stage IVB	Any T	Any N	M1

We recently proposed a staging system, using preoperative imaging and taking into account the extent of biliary ductal involvement, vascular involvement, and lobar atrophy, that may be more applicable than the other systems, given modern surgical therapies (Table 33.5-14).[270] In the era of effective surgical therapy for cholangiocarcinomas, this staging system is a better predictor of resectability and outcome than is the AJCC classification.

Treatment with Curative Intent

The only curative option is complete surgical excision of the cholangiocarcinoma. Until the last decade, such surgical resections were rarely accomplished, because complete excision usually requires a major liver resection, biliary resection and reconstruction and, often, a major vascular resection and reconstruction.[270,334,335] As advances in diagnostic imaging have been made, earlier detection of cholangiocarcinoma and improved operative planning are possible. As surgical techniques have evolved to make major hepatectomies routine, increasing numbers of resections have been accomplished. The results generated over the last decades has firmly established resection as safe and effective treatment and have helped to define patient selection and operative conduct.

RESECTION. It has become clear over the last three decades that curative treatment of tumors involving the upper third of the bile duct very much depends on aggressive surgical excision. Until as recently as one decade ago, surgical treatment of hilar cholangiocarcinomas was associated with a mortality as high as

TABLE 33.5-14. Proposed Staging System for Proximal (Hilar) Cholangiocarcinoma in the Era of Effective Surgical Therapy

T Stage	*Biliary Involvement*	*Ipsilateral Lobar Atrophy*	*Ipsilateral Portal Vein Involvement*	*Main Portal Vein Involvement*
T1	Hilus and/or right or left hepatic duct	No	No	No
T2	Hilus and/or right or left hepatic duct	Yes	No	No
T3	Hilus and/or right or left hepatic duct	Yes/No	Yes	No
T4	Secondary biliary radicles bilaterally	Yes/No	Yes/No	Yes

(Data from ref. 270.)

30%.[333,336–340] Before the 1990s, most surgical series were small, operative mortalities were high, and only a handful of 5-year survivors were reported.[378–385] That this entire disease was regarded with pessimism was understandable.[309,341,342] It is not surprising, therefore, that until recently, the surgical therapy for proximal biliary malignancies consisted mainly of biliary-enteric bypass as palliation for jaundice and cholangitis. Results reported over the last decade, however, have indicated a major improvement in safety of these operations such that resections of hilar tumors can be accomplished (even when liver resections are required) with a mortality of less than 10% (Table 33.5-15).[271,333,337,345] Increasingly large series have been reported that have firmly documented the curative potential of such major resections (see Table 33.5-15). Given that unresected disease is uniformly fatal, usually within 6 to 12 months, surgical resection has become the treatment of choice when possible.

The goals of surgical management for cholangiocarcinomas are eradication of tumor and establishment of adequate biliary drainage. For tumors of the hepatic ducts and the biliary confluence, symptoms often appear late in the course of disease when the lesion has already involved adjacent structures, including the portal vein or adjacent hepatic parenchyma. Complete resection, therefore, usually requires not only biliary resection but also major liver resection and, often, major vascular and biliary reconstruction.

Discussion of the fine details of resections for hilar cholangiocarcinomas is beyond the scope of this chapter. The reader is referred to standard texts of surgical techniques for detailed technical discussions.[126,344,345] Nonetheless, some major points and principles warrant emphasis.

Laparoscopic evaluation should be considered before a formal laparotomy is performed. Metastatic disease is common in patients with hilar cholangiocarcinoma. One-half or more of the patients will have metastatic disease found at surgery.[270,343,346,347] Recent studies suggest that staging laparoscopy combined with laparoscopic US may be useful in hepatobiliary malignancies to find such metastatic disease and thereby prevent unnecessary laparotomies.[318] In our recent series, 50% of unresectable cases were identified as such by laparoscopy.[347] Of the causes of unresectability, laparoscopy was best at identifying peritoneal metastases and noncontiguous liver metastases and was poor at identifying vascular invasion and nodal metastases.[347] Hence, we would recommend a laparoscopic evaluation immediately before laparotomy. We also recommend that the examination concentrate on peritoneal and liver disease and not perseverate on the biliary or nodal extent of disease in the porta hepatis because of low yield and risk of violation and spread of tumor.

Laparotomy then commences with a thorough exploration of the abdomen. The lymph nodes in the porta hepatis and celiac and retropancreatic area are carefully assessed. If there is spread to celiac or retropancreatic nodes, the chance of long-term survival is sufficiently low that resection is ill-advised. Though a segmental bile duct resection and biliary reconstruction are possible in some patients, most require partial hepatectomy to achieve complete tumor clearance. The extent of liver resection should be tailored to achieve tumor clearance. Some patients with small tumors and low bifurcation of the hepatic ducts may be treatable with a central liver resection. Most patients will, however, require either a lobectomy or a trisegmentectomy for resection of tumor. A subset of patients

TABLE 33.5-15. Results of Resection for Proximal (Hilar) Cholangiocarcinoma after 1990

	No. of Cases	*No. Resected*	*Mortality (%)*	*Survival*			
				Median (mo)	1-Y (%)	3-Y (%)	5-Y (%)
Cameron, 1990[343]	96	53 (41%)	2	24	66	21	12
Nimura, 1990[332]	NR	55	6	—	—	55	41
Hadjis, 1990[339]	131	27 (21%)	7	25	76	26	22
Bismuth, 1991[333]	122	23 (19%)	0	24	87	25	—
Baer, 1993[337]	48	21 (44%)	5	36	72	50	—
Guthrie, 1993[384]	69	10 (14%)	10	16	—	—	—
Washburn, 1995[385]	88	59 (67%)	10	23	69	40	11
Su, 1996[386]	162	49 (30%)	10	19	—	—	35
Nakeeb, 1996[290]	196	109 (55%)	4	18	68	30	11
Klempnauer, 1997[362]	339	151 (55%)	10	24	72	40	22
Burke, 1997[270]	90	30 (33%)	6	40	—	—	56

NR, not reported.

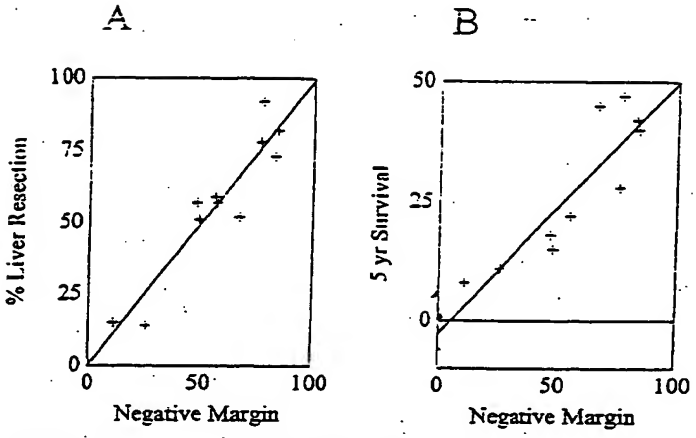

FIGURE 33.5-5. A: Relationship of percentage of liver resection to percentage of margin-negative cases for proximal (hilar) cholangiocarcinomas. Willingness to resect liver is essential for complete excision of cholangiocarcinomas and for achieving negative surgical margins. B: Relationship of percentage of margin-negative cases to percentage of 5-year survivors for proximal (hilar) cholangiocarcinomas. Achieving a negative margin is essential for favorable long-term outcome.

will also require excision of the caudate lobe (segment 1) to clear tumor completely.[348,349]

The factors most influential in predicting recurrence are a margin-positive resection,[350] node-positive tumor,[351] and vascular involvement by tumor. Of these, the only factor over which the surgeon can routinely have influence is the surgical margin. There is now substantial evidence that partial hepatectomy is usually required to achieve a surgical margin clear of tumor. Bile duct excision and partial hepatectomy, often with *en bloc* caudate lobectomy,[352] are frequently necessary to achieve negative margins. Indeed, several recent studies show a parallel between the number of patients undergoing partial hepatectomy and the number of patients with negative margins (Fig. 33.5-5*A*).[270,339,353–355] Furthermore, there is a direct correlation between negative margins and long-term survival (see Fig. 33.5-5*B*). Clearance of tumor is essential for potential cure.[270]

In the era when surgeons were unwilling to perform major liver resections to clear tumor, only the smallest of hilar cholangiocarcinomas could be resected. Given that extensive liver resections are now routine at many major centers, extensive unilobar disease is commonly resected with curative intent. In a recent study, of the 30 patients subjected to resections of cholangiocarcinoma, including 25 (83%) with negative histologic margins, 15 patients had tumor involvement of secondary biliary radicals, 11 had unilateral lobar liver atrophy, and 8 had encasement or occlusion of a major portal vein branch.[270] In the past, these findings would have been considered technically insurmountable.

The entire extrahepatic bile duct should be removed, as this assists in resection of the lymphatic tissues in the porta hepatis. Lymphatic metastases are common,[270] and a complete portal lymphadenectomy is essential. Biliary continuity is then reestablished using a jejunal reconstruction.[356,357] Portal vein invasion by tumor does not rule out resection, long-term survival, or potential cure,[270] provided that the portal vein involvement is unilobar and on the side of the dominant biliary involvement. Bilateral portal venous involvement or unilobar invasion contralateral to extensive biliary invasion usually denotes unresectable disease and, consequently, poor prognosis.

Recent results of resection have shown great improvement over previous results. Median survival is longer than 24 months.[271,335,337] Five-year survival is accomplished in nearly 30% of patients (see Table 33.5-15). Such long-term survival can be achieved with an acceptable operative mortality.[187,270,271,295,313,316,339,352–355,358–362] For those surviving the operative procedure, surgical resection provides not only improved survival but also improved quality of survival.[363]

ADJUVANT THERAPY. To date, no chemotherapeutic regimen has consistently shown activity in cholangiocarcinoma.[364] Although chemotherapy based on 5-FU often is offered to patients with nonresectable disease, the likelihood of response is less than 10% (see later in Chemotherapy and Immunotherapy). There is certainly no proven role for adjuvant chemotherapy in the treatment of cholangiocarcinoma.

The role of radiotherapy in the treatment of resected extrahepatic bile duct cancer is controversial. Given the poor prognosis of patients who have undergone a complete resection (median survival range, 1.5 to 2.0 years) and the fact that many resections leave microscopically positive margins, many practitioners have advocated postoperative irradiation with or without systemic chemotherapy (Table 33.5-16). External-beam doses in the range of 45 to 60 Gy (with the latter doses for positive margins) are usually administered. In addition to external-beam radiation, boost doses can be administered using intraluminal brachytherapy (ILB). In this approach, a wire or string of radioactive seeds (typically ^{192}Ir) is introduced into the bile duct, which delivers 20 to 30 Gy at a 0.5- to 1.0-cm depth. Traditionally, this has been performed using low dose-rate radiation (<1 Gy/h); more recently, high dose-rate radiation (approximately 2 Gy/min) has been administered.[365] The advantage of ILB is the potential to deliver a high dose of radiation to the duct itself with minimal damage to surrounding liver.[366,367] The disadvantage is that disease more than 1 cm from the duct tends to be underdosed. In addition, ILB may be associated with an increased risk of infection.

In two separate reports from Johns Hopkins, no benefit of adjuvant external-beam and intraluminal radiotherapy was demonstrated.[343,368] In contrast, Kamada et al.[369] suggested that radiation may improve survival in patients with histologically positive hepatic duct margins. Additionally, in a small series of patients (five with hilar cholangiocarcinoma) from Louisville, resectability was reportedly greater in patients given neoadjuvant radiotherapy prior to exploration.[370] In a series of 23 patients with cholangiocarcinoma, Urrego et al.[371] used a chemoradiation regimen for adjuvant therapy, consisting of postoperative irradiation, 5-FU, leucovorin, and IFN. The 5-year survival was 53%.[371] These results certainly encourage further study of radiotherapy with or without chemosensitization in the adjuvant treatment of cholangiocarcinoma. Given the small size of the studies and lack of randomized trials, the utility of radiotherapy, and particularly ILB, is far from proven. In our practice, adjuvant therapy is generally used only if there is a positive margin or in the setting of metastases to lymph nodes. Other patients are not offered adjuvant therapy.

LIVER TRANSPLANTATION. Orthotopic liver transplantation has been attempted for unresectable hilar tumors. Klempnauer et al.[372] reported 4 long-term survivors of 32 patients submitted to transplantation for hilar cholangiocarcinoma.

TABLE 33.5-16. Results of Adjuvant Radiotherapy in Patients with Resected Cholangiocarcinoma

Study	Schedule	Radiotherapy: Dose	Radiotherapy: No. of Patients	Chemotherapy	Median Survival (mo)
Pitt[213]	Postop (includes positive margins)	40–60 Gy ± ILB (2–18 Gy)	14	None	20
		None	17	None	20
Urrego[371]	Preop[a] (complete resection)	49.5 Gy (median)	23	Chiefly 5-FU	NA[d]
Gonzalez[407]	Postop[b] (includes positive margins)	50 Gy (mean)	30	None	24
		45 Gy (mean) + 22–25 Gy ILB	41		24
Kurosaki[587]	IO + Postop	40 Gy + 20 Gy IO (median)	35	None[c]	19
McMasters[370]	Preop	45–50.4 Gy	9	5-FU by infusion	22
	Postop	45–50.4 Gy	20	5-FU by infusion	22
		None	11	5-FU by infusion	22

5-FU, 5-fluorouracil; ILB, intraluminal brachytherapy; IO, intraoperatively; NA, not available; Postop, postoperatively; Preop, preoperatively.
[a]Orthotopic liver transplantation in 17 patients.
[b]Nineteen patients received 10.5 Gy preoperatively.
[c]Four patients received unspecified chemotherapy.
[d]Five-year survival, 54%.

Comparable results were reported by Iwatsuki et al.[573] These results do not justify the use of precious organs when many patients with benign disease are dying awaiting liver transplantation. Therefore, most centers do not currently perform liver transplantation for cholangiocarcinoma.

Palliative Treatments

Patients with hilar cholangiocarcinoma most often die from liver failure due to tumor progression or from sepsis due to biliary infection. If resection is not feasible, then palliative treatment must be directed first and foremost at preventing or relieving biliary infection. Secondarily, palliative antitumor treatments such as radiotherapy or chemotherapy should be considered, though neither of these modalities has been clearly proven to prolong survival significantly.

BILIARY DRAINAGE. The important concept in the prevention of biliary sepsis is the understanding that jaundice alone is not necessarily an indication for biliary decompression. Unlike biliary obstruction in the lower bile duct, where a single stent usually effectively relieves the biliary obstruction, biliary obstruction near the hilus is much more difficult to relieve. Even with a small tumor, a single stent likely will drain only one-half of the liver. When the tumors are large and involve second- or third-order bile ducts, many stents may be required to provide effective biliary decompression; it is also possible that effective biliary decompression cannot be achieved in such cases. Biliary manipulation of any kind may therefore introduce bacteria into the biliary tree and cause sepsis that may not subsequently be fixable.

Good indication for biliary drainage must exist before attempts are made. Our current indications for biliary decompression in inoperable patients are intractable pruritus, cholangitis, the need for access for intraluminal radiotherapy, or the need for drainage for administration of chemotherapeutic agents. When none of these indications exists, the patient is probably better served by avoiding biliary manipulation. Supportive care alone is probably the best approach, particularly for elderly patients with significant comorbid conditions.

Unfortunately, most patients present to a tertiary care center already having undergone manipulation of the biliary tree. Most of these patients, therefore, have bacterbilia and, possibly, overt sepsis, and drainage of the biliary tree is an essential part of the therapy to prevent immediate life-threatening complications.

Biliary drainage can be accomplished nonsurgically or surgically. Nonsurgical drainage is preferred if the patient has significant comorbid conditions or if the tumor as evaluated by preoperative imaging is clearly not resectable for cure. Though biliary decompression can theoretically be accomplished either by percutaneous transhepatic puncture or by endoscopic stent placement, hilar tumors are notoriously difficult to traverse with the endoscopic technique. Moreover, the failure rates and incidence of subsequent cholangitis are high.[574] Thus, most patients with unresectable hilar tumors are not candidates for endoscopic biliary drainage. Percutaneous transhepatic biliary drainage and subsequent placement of a self-expandable metallic endoprosthesis (Wallstent, Boston Scientific, Boston, MA) is the palliative procedure of choice for these patients. However, as mentioned, satisfactory results are more difficult to achieve in patients with hilar tumors than in those with distal biliary obstruction.[277,375,576] Frequently, hilar tumors isolate the liver into multiple obstructed biliary units, and two or more stents must be placed for adequate drainage.[577] Portal venous involvement and consequent hepatic lobar atrophy may also complicate drainage procedures, as drainage through an atrophic lobe usually does not relieve jaundice. Furthermore, a stent placed for a hilar obstruction is associated with a substantially higher rate of occlusion than that placed in the distal duct.[277,578] Therefore, most patients will require multiple manipulations of their stents placed for hilar obstruction.[277,377–382] These difficulties also explain the high periprocedural mortality in this patient population: 14% at 30 days.[380]

Biliary enteric bypass is a surgical alternative to percutaneous placement of an endobiliary prosthesis. Certainly, patients whose tumors are found to be unresectable at operation should be con-

TABLE 33.5-17. Results of Chemotherapy for Biliary Tract Tumors (Cholangiocarcinomas or Gallbladder Cancers)

Study	*No. of Cases*	*Treatment*	*PR*	*Stable Disease*
Davis, 1974[589]	23	5-FU	3 (13%)	NR
Haskell, 1980[590]	17	5-FU	2 (11%)	NR
Falkson, 1985[586]	30	5-FU	3 (10%)	NR
Crooke, 1976[592]	15	Mitomycin C	7 (47%)	NR
Taal, 1993[484]	30	Mitomycin C	3 (10%)	NR
Okada, 1994[593]	13	Cisplatin	1 (8%)	NR
Jones, 1996[590]	14	Paclitaxel	0	2
Mezger, 1997[596]	11	Gemcitabine	0	6 (54%)
Raderer, 1999[594]	19	Gemcitabine	3 (16%)	4 (21%)
Falkson, 1985[586]	26	5-FU + streptozotocin	2 (8%)	NR
Falkson, 1985[586]	31	5-FU + MeCCNU	3 (10%)	NR
Patt, 1996[589]	18	5-FU + IFN	6 (34%)	NR
Chen, 1998[595]	18	5-FU (high-dose) + LV	6 (33%)	7 (39%)
DeGusmao, 1998[597]	14	5-FU + gemcitabine	6 (43%)	NR
Rougier, 1995[596]	18	5-FU, cisplatin, CI	6 (24%)	NR
Di Lauro, 1997[595]	15	5-FU; cisplatin, epirubicin	5 (33%)	5 (33%)
Harvey, 1984[591]	13	5-FU, mitomycin C, doxorubicin	4 (31%)	7 (53%)
Sanz-Altamira, 1998[594]	14	5-FU, LV, carboplatin	3 (21%)	4 (28%)
Raderer, 1999[594]	20	5-FU, LV, mitomycin C	5 (25%)	6 (30%)
Hall, 1979[597]	8	Doxorubicin + BCNU + tegafur	3 (38%)	1 (13%)
Isacoff, 1993[596]	7	5-FU, mitomycin C, doxorubicin, CI	3 (43%)	NR
Kajanti, 1994[599]	22	5-FU, LV, methotrexate, epirubicin	0	NR

CI, continuous infusion; 5-FU, 5-fluorouracil; IFN, interferon; LV, leucovorin; MeCCNU, semustine; NR, not reported; PR, partial response.

sidered for such bypasses,[270] because they will have already incurred the morbidity of laparotomy. Patients with small, unresectable, but well-localized disease are particularly good candidates for biliary enteric bypass, as this allows access to the biliary tree for ILB.[583] Typically, segment III bypass is used.[584] Relief of jaundice will be achieved if at least one-third of the functioning hepatic parenchyma is adequately drained. Additional percutaneous stenting to reestablish biliary continuity of the two sides of the liver is required if the bypass is to an atrophic or a small lobe or if infection has occurred in the contralateral lobe of liver.[585] In our recent report of 55 consecutive bypasses in patients with malignant hilar obstruction, segment III bypass yielded a 1-year bypass patency of 80%, and there were no perioperative deaths.[584]

CHEMOTHERAPY AND IMMUNOTHERAPY. Many different chemotherapeutic regimens have been investigated in small uncontrolled studies, with generally poor results (Table 33.5-17). A study by the European Organization for Research and Treatment of Cancer testing mitomycin C on patients with gallbladder and biliary carcinomas showed a response rate of 10% (3 of 30). The group also compared oral 5-FU to 5-FU with either streptozotocin or MeCCNU in patients with gallbladder or biliary duct cancer and demonstrated a similarly low response rate of 9%, with no differences in the types of drugs used.[586] Some of the newer drugs have also not demonstrated significant efficacy as single-agent therapy. Paclitaxel demonstrated no activity in 15 patients with biliary carcinoma,[587] and a phase II study of docetaxel likewise demonstrated no activity.[588]

Combinations of various chemotherapeutic agents have been tested, with mixed and conflicting results. Patt et al.[589] used 5-FU and IFN as combined therapy for patients with cholangiocarcinoma. Of 32 patients, 11 (34%) had a partial response, with a median time to disease progression of 9.5 months and a median survival of 12 months.[589] However, another phase II study analyzing the effect of 5-FU combined with IFN-α_{2b} and paclitaxel failed to show any benefit.[590] In one study combining 5-FU, mitomycin, and doxorubicin, 31% of patients responded,[591] whereas in another trial, there were no responses among 18 patients.[592] The combination of 5-FU, cisplatin, and epirubicin produced a 33% response rate in 15 patients with biliary tract carcinoma in an Italian study,[595] and 5-FU, leucovorin, and carboplatin produced a 21% response rate among 14 patients.[594] Rougier et al.,[596] using continuous-infusion 5-FU and cisplatin, produced a 33% response rate in 18 patients. Gemcitabine[596] and 5-FU plus gemcitabine[597] have also been tested and, in one study involving 14 patients, 42% responded.[597] At present, either 5-FU and cisplatin or 5-FU and gemcitabine must be considered the regimens of greatest promise in the palliative treatment of unresectable cholangiocarcinoma. We tend to use the latter combination because of its lower toxicity as compared to the former.

The blood supply to the biliary tree is derived primarily from the hepatic artery. Therefore, attempts have been directed at delivering chemotherapeutic treatment via hepatic arterial infusion to patients with cholangiocarcinoma. In one study of 11 patients (4 with cholangiocarcinomas and 7 with gallbladder cancers), hepatic infusion of 5-FU and mitomycin produced 7 responses but a median duration of response of only 3 months and a median survival of 12.5 months.[598] Reed et al.[599] reported seven significant regressions in nine patients with biliary carcinoma treated with intraarterial FUDR. This approach is far from proven and, at present, operative intervention to implant an arterial infusion pump for delivery of regional chemotherapy should be performed only in the investigational setting.

Tamoxifen is a potential MDR-reversing agent[161] and has been shown to inhibit human cholangiocarcinoma cell lines.[400] No clinical data exist, however, to indicate whether this may be a reasonable therapeutic modality for patients with unresectable cholangiocarcinomas.

PALLIATIVE RADIOTHERAPY. External-beam irradiation with or without ILB has also been used for palliation of patients with unresectable perihilar bile duct cancer. External-beam irradiation is usually delivered to a dose of 5000 to 6000 cGy. ILB most often uses ^{192}Ir (2000 cGy) delivered percutaneously. Several authors have demonstrated the feasibility of radiotherapy in small, nonrandomized trials.[343,383,401–404] However, to date, no study has clearly demonstrated efficacy for this modality. In a group of 12 patients treated with a combination of endoluminal and external-beam radiotherapy, the median survival was 15 months. Though episodes of cholangitis and intermittent jaundice were relatively common, the incidence of serious complications was low, and there were no treatment-related deaths.[383] Cameron et al.[343] reported improved survival in irradiated patients as compared to a group of patients who were not irradiated; however, the median survival in both groups was less than 1 year. Others have reported no benefit of radiotherapy in this setting and question its routine use, given the increased incidence of complications and the greater time spent in hospital.[401] Certainly, radiotherapy has not been shown to produce improved survival as compared with biliary decompression in randomized, controlled trials. Though anecdotal reports of long-term survivors after external-beam radiotherapy show that some individuals may benefit from such treatment, such potential benefit must be weighed against the possible complications, such as duodenal or bile duct stenosis and duodenitis.

Evidence in the literature supports using fluoropyrimidines as radiosensitizers, and chemoradiotherapy is used as standard therapy for a number of other tumor types. For bile duct cancers in particular, however, evidence supporting the use of chemoradiotherapy is sparse. In a study conducted by the Eastern Cooperative Oncology Group, 16 patients with pancreatic carcinoma and 9 with bile duct cancers were treated with a combination of 5-FU (200 mg/m^2/d) and concurrent radiotherapy (59.4 Gy). The entire group had a median survival time of 11.9 months. Unfortunately, 15 of the 25 patients had clinical or radiographic evidence of progression of disease at the site of the primary tumor, which was in the radiotherapy port.[405] Moreover, median survival for the patients with locally advanced, unresectable disease that was treated with radiotherapy with or without systemic chemotherapy tends to be less than 1 year.[273,370,371,401,406–408] Our current practice is to use combined interstitial irradiation and external-beam irradiation in patients with very limited, locally unresectable disease, when there are no indications of distant spread. Multicenter, randomized trials are in order for this subpopulation. Radiotherapy is clearly inappropriate in patients with widespread disease.

PERIPHERAL CHOLANGIOCARCINOMA

Peripheral or intrahepatic cholangiocarcinoma is another rare disease, accounting for 1000 to 2000 cases per year in the United States.[409] Clinical presentation is similar to that for HCC, with the most common symptoms being right upper quadrant pain, epigastric pain, and weight loss.[287,409] Jaundice occurs in only 24% of patients with peripheral cholangiocarcinoma as compared with 71% of patients with hilar or Klatskin tumors.[409] Because the tumor is usually asymptomatic in its early stages, most patients have advanced disease at presentation. On cross-sectional imaging by CT or MRI, the peripheral cholangiocarcinoma usually is confused with HCC or metastatic tumor from an unknown primary source. Unlike HCC, AFP levels will be normal. A search for alternative primary cancers that may have produced a liver metastases will not be fruitful. A solitary lesion not associated with the gallbladder in a patient with no cirrhosis and no other primary cancer and with a normal serum AFP should raise suspicion of a peripheral cholangiocarcinoma. However, intrahepatic metastases and tumor growth along the biliary tract frequently occur. When multiple tumors are found, it is even more difficult to distinguish these tumors from metastatic disease originating from a distant site.

Lymph node involvement is more common with peripheral cholangiocarcinoma with hilar bile duct tumors. In a series of 65 peripheral and 27 hilar cholangiocarcinomas, Nakajima et al.[410] found lymph node involvement in 86% of peripheral tumors as compared with 33% of hilar tumors. Intrahepatic and systemic metastases were found in 68% and 71%, respectively. The TNM staging of intrahepatic or peripheral cholangiocarcinoma is the same as that for HCC.

Conventional surgical resection, when possible, is the treatment of choice. In a series of 42 patients with peripheral cholangiocarcinoma, Altaee et al.[336] reported that survival was indistinguishable from that of 70 patients with hilar cholangiocarcinomas. The median survival was 12 months, and no patient survived more than 42 months. Others have reported more favorable results. Chen et al.[409] reported on 20 patients with peripheral cholangiocarcinoma undergoing surgery over a 10-year period who had a median survival of 21 months. Four patients lived more than 3 years, and one patient was alive 5 years after resection. In our own report of 32 cases of resected peripheral cholangiocarcinoma, median survival was 59 months, with an actuarial 5-year survival of 42%. Vascular invasion and intrahepatic satellite lesions were predictors of worse survival ($P < .05$).[287]

The few data available concerning results of liver transplantation for this disease have not been encouraging. Penn[259] reported a 17% actuarial 5-year survival rate for 109 intrahepatic and extrahepatic cholangiocarcinoma patients who received liver transplants at various centers throughout the world. In this series also, there was no significant difference between the recurrence rates of hilar and peripheral tumors.

Data for chemotherapy or radiotherapy in treating this disease is even more sketchy. Stillwagon et al.[411] reported a 5% complete response and 46% partial response for the treatment of peripheral cholangiocarcinoma with a regimen of initial whole liver irradiation to 2100 cGy in seven fractions and doxorubicin, cisplatin, and ^{131}I anti-CEA antibody.[411] Although the median survival was 14 months from diagnosis and 10 months from treatment, no patient survived more than 2 years from the start of therapy.

TUMORS OF THE GALLBLADDER

Alfred Blalock recommended in 1924 that ". . . in malignancy of the gallbladder when a diagnosis can be made without exploration, no operation should be performed, inasmuch as it